

**An Investigation Into The Mechanisms, Consequences and Moderators
of Intradialytic Hypotension in Paediatric Haemodialysis**

By

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I, Daljit K Hothi confirm that the work presented in this thesis is my own.
Where information has been derived from other sources, I confirm that this
has been indicated in the thesis.

Daljit K Hothi

*I would like to dedicate this to my husband Saj
and my mum Pal.*

Thank you for both for all your love and unconditional support.

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Publications arising from this work

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- Pediatric Myocardial Stunning Underscores The Cardiac Toxicity Of
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- The Value Of Sequential Dialysis, Mannitol And Midodrine In Children Prone
To Dialysis Failure
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Contributions made to this thesis

Dr Daljit K Hothi designed the studies, recruited the subjects and conducted the trials.

Blood samples were drawn by the dialysis unit staff and then sent by Dr Hothi to the laboratories affiliated to the hospitals at Great Ormond Street, London or Hospital for Sick Children, Toronto.

Echocardiograms for the analysis of regional wall motion abnormalities were reviewed by Dr James Burton for suitability but all the analyses were conducted by Dr Hothi. Echocardiograms analysed with two-dimensional speckle tracking for peak longitudinal, radial and circumferential strain were reviewed by Dr Marek for suitability and analysed by Dr Hothi. Echocardiograms for normal age matched controls were taken by the echocardiography technicians at Great Ormond Street Hospital and then all the images were analysed by Dr Hothi.

Abstract

The relationship between hypertension and cardiovascular morbidity has long been recognised. However evidence is mounting implicating hypotension and not hypertension as the predominant risk factor for mortality. I demonstrated a 20-30% prevalence of intradialytic symptoms and hypotension in children during conventional, 4 hour haemodialysis (HD) sessions. The declining blood pressure (BP) was originally believed to be caused by ultrafiltration (UF) and priming of the HD circuit due to loss of fluid from the intravascular space. However data, largely in adults, challenged this hypothesis leading to a new consensus that intradialytic hypotension has a multifactorial aetiology. The uraemic milieu triggers a series of events that alters the cardiovascular compensatory responses to haemodynamic stresses, however the extent to which these physiological responses are impaired and their consequences are unknown and poorly understood.

At first I corroborated adult findings that a poor correlation existed between relative blood volume changes and intradialytic hypotension in children, supporting the theory that fluid removal alone was not responsible for cardiovascular decompensation during HD and this assumption was a gross oversimplification of the underlying problem. Using a traditional method (endocardial wall motion) and a novel method (Speckle tracking 2-dimensional strain) I then measured the regional left ventricular (LV) function in children (aged 2 to 17 years) at the start of dialysis and again during peak stress at the end of HD. I found rising cardiac troponin I levels in 25% of the cohort and reduced regional LV function in all the children examined. The level of dysfunction significantly correlated with actual BP, the degree of intradialytic BP fall and UF volumes. What remains unclear however is whether the fall in BP was the cause or effect of the ischaemic cardiac injury. Finally I investigated dialysis methods for abrogating intradialytic morbidity in children treated with four hour HD sessions. A step sodium profile from 148mmol/l to 138mmol/l, prophylactic mannitol and sequential dialysis were successful, to variable degrees in attenuating intradialytic symptoms or hypotensive episodes. Intradialytic midodrine was exclusively used in one patient resistant to all other forms of therapy and was found to be the most efficacious in supporting the BP and preventing hypotension.

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Chapter One

Introduction: Intradialytic Hypotension

1.1 Epidemiology

During haemodialysis (HD) the objective is to remove all the sodium and water that accumulates in the inter-dialytic period within the few hours of treatment time. The major barrier to achieving this goal is the development of haemodynamic instability, manifesting as hypovolaemia related symptoms or intradialytic hypotension. In adults this occurs on average in 20-30% treatments¹ with a resultant risk of under dialysis from recurrent treatment interruptions and patients remaining volume overloaded. There is a clear correlation between high blood pressure (BP) and the risk of stroke. Several observational studies in patients with essential hypertension also describe a “J” shaped curve between diastolic blood pressure (BP) and mortality². The same trend has been described in dialysis patients, with a suggestion that hypertension is associated with morbidity but mortality is associated with hypotension³. In adults, patients with pre-dialysis systolic BP less than 110 mmHg have a fourfold increase in the relative risk of cardiac-related death versus those with a systolic BP between 140 to 149 mmHg. Post dialysis, patients with systolic BP less than 110 mm Hg had a 2.8-fold increase in relative risk for a cardiac-related death compared with patients with systolic BP 140 to 149 mmHg⁴ (see Figure 1.1). The difficulty in dialysis patients is establishing accurate surrogates of interdialytic BP load. Most commonly BP targets are based solely on pre- and/or post-dialysis systolic BP measurements, however Agarwal et al have shown a steady rise in systolic and diastolic BP during the interdialytic period that reaches a plateau 48 hours after dialysis⁵. Furthermore both pre- and post-dialysis BP measurements were found to be inferior to home BP recordings in predicting left ventricular hypertrophy and mortality⁶. One could therefore postulate that the negative association between low BP and adverse outcomes only reflects the use of a poor

surrogate marker of afterload or may represent a cohort of patients with cardiac dysfunction or impaired cardiovascular reserve during times of stress.

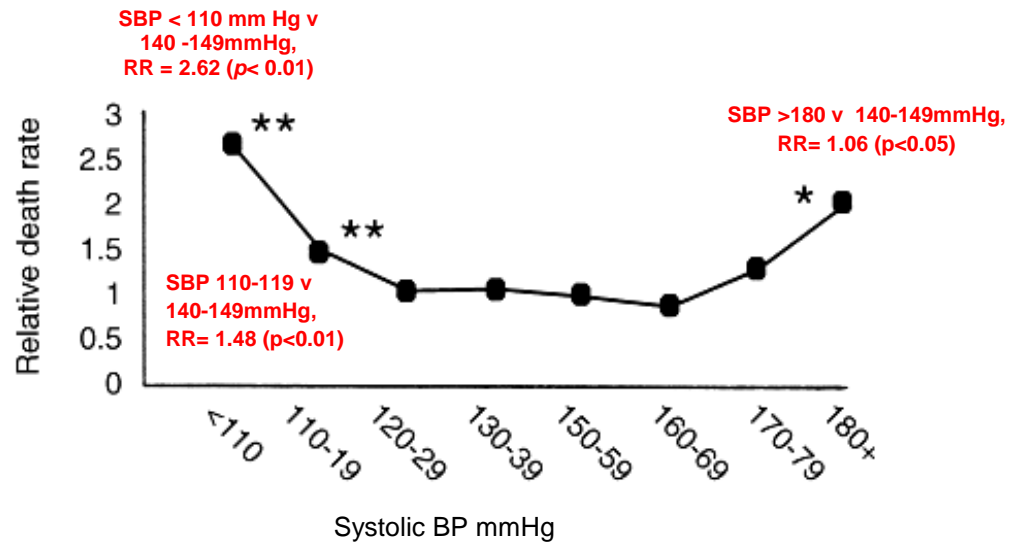


Figure 1.1: Systolic blood pressure (SBP) post dialysis and cardio/cerebrovascular mortality in haemodialysis patients⁴

Frequent intradialytic hypotensive episodes have also been implicated in accelerating decline in residual renal function and precipitating serious vascular complications such as cerebral, cardiac and mesenteric ischaemia. The problem is confounded in children as the ultrafiltration (UF) goal is often higher from liquid nutritional supplements or poor adherence to fluid restrictions. In addition younger or developmentally delayed children may not be able to verbalize the evolution of new symptoms and therefore there can be very little warning of decompensation. This places a greater reliance on monitors and basic cardiovascular measurements during their treatments.

1.2 Definition

There is no recognised definition of intradialytic hypotension in children. Very loosely the term refers to a drop in BP during dialysis and has been defined by KDOQI as a decrease in systolic blood pressure by ≥ 20 mm Hg or a decrease in MAP by 10 mm Hg associated with symptoms⁷. The former is such a non-specific, subjective definition and unsuitable in the research arena. The latter in our opinion is not always relevant in the paediatric environment. In children the evolution of symptoms can be for a number of reasons but if a hypertensive patient had a 25mmHg fall in systolic BP that restores their BP to within the normal range, despite being a clinically a favourable outcome this will still be categorised as an episode of intradialytic hypotension and thus a negative dialytic outcome. Therefore at the onset of this work I elected to develop a clinically valid, objective and reproducible definition relevant to paediatrics.

The first task force on blood pressure control in children is the only group to report age and gender adjusted 5th percentile systolic blood pressure measurements from the general population⁸. For the purpose of this study, I defined intradialytic hypotension as any BP measurement below the 5th percentile systolic blood pressure measurements as this is equivalent to a BP below that expected within the normal population. Any deviation from this is clearly stated in the text.

1.3 Pathophysiology

During dialysis mobilization of fluid from the interstitial to the intravascular space, venoconstriction of capacitance vessels, increased vascular tone and active increases in heart rate and contractility preserve circulatory adequacy. As a result even with a UF

volume equal to the entire plasma volume the measured blood volume only changes by 10-20%. An impaired compensatory response causes hypotension in the face of total body water expansion.

Most of the plasma volume resides in the veins, with a marked difference in the venous capacitance between organs. During UF the ability to mobilize blood from the splanchnic venous pool is vital for preserving the central blood volume. Venous tone is affected by vasoactive hormones, sympathetic nervous system and upstream filling pressures. The De-Jager Krogh phenomenon refers to the transmission of upstream arterial pressure through the capillaries to the veins causing venous distension and altered venous capacitance. During arteriolar constriction the distending pressure to the vein is reduced and blood is extruded centrally towards the heart to maintain cardiac refilling. Conversely factors that cause arterial dilatation, such as antihypertensives increase venous capacitance, reduce cardiac filling pressures and through transmission of increased hydrostatic pressure to the capillary bed inhibit vascular refilling.

Vasoconstriction is mediated by an increase in sympathetic activity. In dialysis patients this response can be inadequate owing to an increased production of vasodilators or impaired sympathetic response to hypovolaemia. Adenosine is an endogenous vasodilator that is released by vascular myocytes and endothelial cells. It is hypothesized that during a sudden, non-gradual intradialytic hypotension episode, ischaemia prevails resulting in increased consumption of adenosine triphosphate (ATP) and generation of adenosine⁹. This is thought to augment splanchnic blood pooling through an inhibitory effect on norepinephrine release thus causing regional vasodilatation, result in arteriolar vasodilatation and depress myocardial contractility. In

fact, pretreating hypotensive prone patients with caffeine, an adenosine receptor antagonist, was shown to lower the number of hypotensive episodes in adults¹⁰. Additional mediators of tone include nitric oxide and asymmetrical dimethyl arginine (ADMA). During dialysis elevated levels of cytokines such as interleukin 6 and tissue necrosis factor alpha stimulate synthesis of inducible nitric oxide synthetase within vascular smooth muscle cells and thus an increased production of nitric oxide, a potent vasodilator. However the increase in nitric oxide concentration is delayed by hours after the initial exposure to the cytokines and is also accompanied by the continued removal of competitive inhibitors of nitric oxide synthetase such as ADMA¹¹ during HD. Such enhancement of endothelial function hours into dialysis is thought to contribute to the evolution of late onset intradialytic hypotension.

The sympathetic nervous system is the principle control mechanism of arteriolar tone and therefore of central blood pressure and patients with end stage renal disease (ESRD) show increased basal level of peripheral sympathetic activity^{10, 12}. In hypotensive prone patients a paradoxical decrease in sympathetic activity is seen at the time of a hypotensive episode¹² and this results in a rapid decline in the peripheral vascular resistance and increased vascular bed capacitance. Problems with sympathetic end-organ responsiveness and the efferent parasympathetic baroreceptor pathway have also been reported but the underlying mechanism remains unexplained. Some believe this may be a heightened manifestation of the Bezold-Jarisch reflex, a cardiodepressor reflex resulting in a sudden loss of sympathetic tone causing abrupt severe hypotension accompanied by bradycardia. It is postulated that conditions associated with reduced cardiac refilling pressures such as left ventricular hypertrophy, diastolic dysfunction or

structural heart defects stimulate cardiac stretch receptors and thus maladaptively trigger a variant of the Bezold-Jarisch resulting in hypotension.

The remaining key player and interconnecting component is plasma refilling. This refers to the movement of fluid from the extravascular to the vascular compartment under the influences of hydraulic, osmotic and oncotic pressure gradients across the capillary bed. If UF rates exceed refilling rates the intravascular volume will fall. There is evidence of increased capillary permeability in the presence of uraemia that encourages movement of water between the interstitium and intravascular compartments¹³. Arterial vasoconstriction decreases hydrostatic pressures on the capillary bed, facilitating vascular refilling. The oncotic pressure which is effectively the plasma protein concentration promotes refilling; and plasma sodium and glucose mobilizes fluid from the intracellular space as a result of increased plasma tonicity¹⁴. Plasma haematocrit level has a positive influence on refilling rates, however during dialysis plasma haematocrit levels change as early as 15mins secondary to change in posture, haemodilution caused by redistribution of water from the extra- to the intravascular space and redistribution of blood from the microcirculation to the central circulation, the Fahraeus effect¹⁵. Finally refilling is facilitated by greater tissue hydration and occurs at a faster rate when the interstitial space is overloaded.

There are also a number of additional factors that may influence the central blood pressure during dialysis. Firstly the volume of blood that is required to support the extracorporeal circuit can be a significant proportion of the effective circulating volume in the younger patients. Blood and dialyser membrane reactions can result in a significant inflammatory response and early decompensation, with some evidence

suggesting cellulosic membranes to be greater offenders in activating complement and a number of cytokine systems than synthetic membranes. The choice of anticoagulant can also influence intradialytic BP with reports of hypotension with regional citrate and prostanoid anticoagulation compared with heparin and low molecular weight heparins.

In essence we know that hypovolaemia is the trigger for intradialytic hypotension but the pathophysiology is complex and the current explanation is incomplete. The uraemic milieu impairs compensatory responses to reduced blood volume with ineffective venoconstriction, inadequate cardiac refilling, reduced plasma refilling and activation of the sympathoinhibitory Bezold–Jarish reflex leading to sudden hypotension. The literature is dominated by research in adults and the degree to which this can be extrapolated to paediatrics is unknown. We have anecdotal evidence that children on conventional HD regimens develop intradialytic hypotension but lack published data on the prevalence, pathophysiology and consequences of intradialytic hypotension that is specific to paediatrics

1.4 Risk Factors

1.4.1 Dialysis Related

The dialysate composition can influence cardiovascular stability during HD. Dialysate sodium generates a crystalloid osmotic pressure and promotes fluid shift between the different body compartments. Dialysate sodium activity is approximately equal to 97% of the measured sodium concentration, but varies with changes in dialysate temperature, pH and the presence of additional ions. In the absence of UF, we can approximate the concentration of dialysate sodium to achieve isotonic dialysis by correcting the blood

sodium measured by direct ionometry for a Donnan factor of 0.967. Hyponatric dialysis causes osmotic fluid shift from the extracellular to intracellular compartment, dialysis disequilibrium disorder and intradialytic hypotension. Hypernatric dialysis transfers sodium to the patient, causing interstitial oedema, interdialytic thirst and increased interdialytic weight gain but may also achieve short-term dialysis gains by improving cardiovascular stability.

Hypocalcaemia depresses myocardial contractility and reduced vascular reactivity¹⁶ and thus increases the risk of intradialytic hypotension. Conversely owing to fear of inducing extra-skeletal calcium deposition, the new K/DOQI guidelines suggest maintaining plasma calcium levels in the low normal range. Using a dialysate calcium concentration of 1.25mmol/l permits higher vitamin D and calcium based phosphate binders in the management of hyperparathyroidism. In a proportion of patients this can lead to hypocalcaemia¹⁷. Low magnesium dialysate baths will encourage the movement of plasma magnesium molecules across the dialysis membranes. Low plasma magnesium levels can result in cramping and arrhythmias and higher magnesium baths may help to improve cardiovascular stability and intradialytic symptoms. Acetate was originally used as the buffer in dialysate as it was cheap, offered equimolar conversion to bicarbonate and is bacteriostatic. However high plasma acetate levels result in vasodilatation, depressed left ventricular function and thus place individuals at risk of intradialytic hypotension and hypoxaemia particularly in the first hour of dialysis¹⁸. Switching to bicarbonate buffers improves cardiovascular stability.

During fluid removal from the vascular compartment venoconstriction of the splanchnic and possibly the splenic¹⁹ vascular beds, mobilizes blood, forcing it centrally towards

the heart to maintain cardiac refilling. If food is consumed during dialysis, blood is diverted to the splanchnic circulation and patients are susceptible to intradialytic hypotension.

1.4.2 Uraemic Cardiovascular Disease

The cardiovascular mortality rate of children and young adults on dialysis is extremely high, at 1000 times greater than age-matched controls²⁰ and greater than adult dialysis patients.

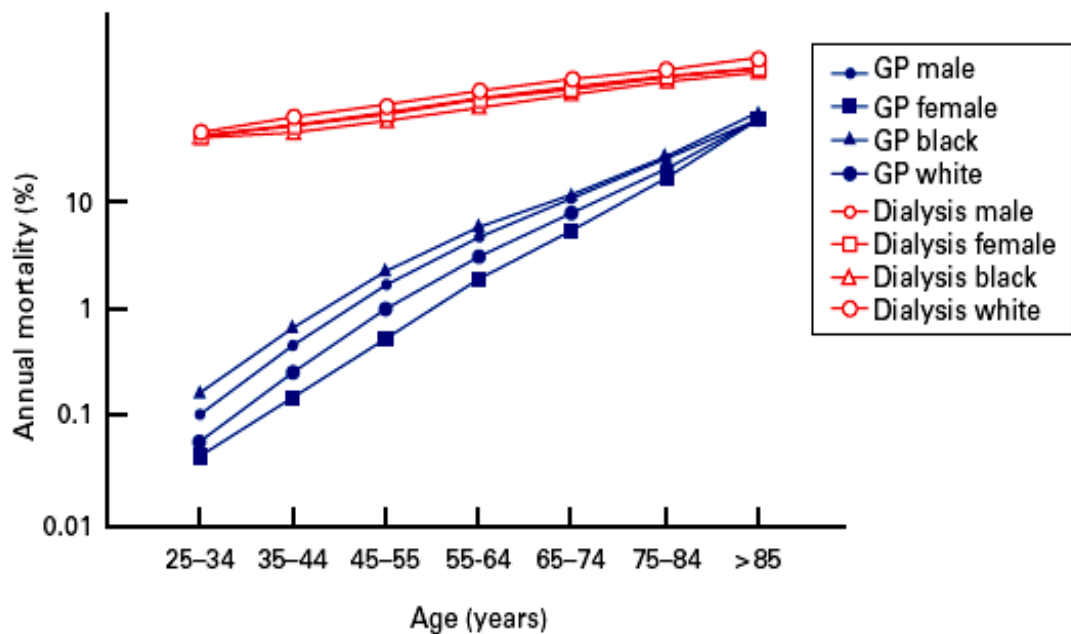


Figure 1.2: All cause cardiovascular mortality for men and women in the general population and those on haemodialysis²⁰

The pathophysiology of uraemic cardiac disease is not fully defined but patients with ESRD are exposed to a number of traditional and non-traditional cardiovascular risk factors. Cardiovascular morbidity and mortality was originally thought to be a problem exclusive to adult dialysis patients however opinions are changing. Children in ESRD share the full gamut of uraemia related cardiovascular abnormalities as adults but

distinct differences exist that may be important in the context of considering cardiovascular stability during HD.

Children do not share the high prevalence of traditional Framingham risk factors as adults and neither have they developed significant classical, atheromatous, coronary and peripheral artery disease. What is unclear however is whether the absence of macroscopic, atheromatous vasculopathy translates to improved dialysis morbidity over adults. Theoretically with less advanced cardiovascular disease children should be able to tolerate larger UF goals without decompensation and tolerate a more aggressive approach towards UF without running the risk of adverse ischaemic injury. However there is clear evidence of significant cardiovascular disease in children on dialysis. Mechanical or haemodynamic overload^{21, 22} and altered humoral responses^{23, 24} are precursors for cardiac remodeling and the development of left ventricular hypertrophy (LVH). Echocardiogram studies have demonstrated significantly worse diastolic dysfunction in children on HD and peritoneal dialysis (PD)²⁵⁻²⁷ compared with those with mild-to-moderate chronic kidney disease (CKD) or post transplant^{27, 28} but the systolic function is preserved. The presence of vascular disease is demonstrated by reports of reduced vascular compliance^{29, 30} and recent studies describing transformation of paediatric vascular smooth muscle cells into osteoblast-like cells with subsequent calcification of coronary valves, carotid and coronary arteries and increased vessel intima-media thickness³¹⁻³³. These vascular abnormalities are accepted markers of asymptomatic atherosclerosis and predictors of future symptomatic CVD in adults with CKD^{34, 35} and although no such data exists in paediatrics it raises a strong suspicion for a maladaptive cardiovascular system in children.

Over and beyond the presence of uraemia, there is now a growing body of evidence incriminating HD as an independent contributor to endothelial dysfunction. HD is pro-inflammatory presumably due to an immune mediated response to non-biocompatible membranes, blood contact with non-sterile dialysate solution and/or "back-leaking" of dialysate across the membrane. However the mechanisms by which CRP production is stimulated still eludes us. More frequent dialysis therapies are associated with improved CRP levels and other markers of inflammation^{36, 37} but in contrast during conventional HD elevated C-reactive protein (CRP) levels correlate with dialysis vintage³⁸. Not only is CRP a valid marker of cardiovascular impairment and atherosclerosis in ESRD but is itself thought to be pathogenic. It is produced specifically by coronary artery smooth muscle cells and directly contributes to vascular inflammation and atherosclerosis³⁹.. Finally HD is also associated with changes in blood volume, blood viscosity and laminar shear stress. This is an environment conducive to disordered endothelial cell dynamics and function and ischaemic injury.

Cardiovascular disease in paediatric dialysis patients is driven by a variety of factors different to those in the general population: peripheral vascular changes, calcification, inflammation and possibly the dialysis procedure itself. However it is difficult to distinguish what is cause or effect in the evolution of intradialytic hypotension and what part, if any, repetitive HD induced ischaemic injury plays in the pathogenic process in children.

1.5 Paediatric Haemodialysis

Technically paediatric HD refers to the dialysis of children from birth to 18 years of age. The basic principles of dialysis are universal but the dialysis prescription has to be tailor-made for each child and is often adjusted according to the patient's body surface area. A conventional paediatric HD schedule consists of four hour treatments, 3 times per week or three hour treatments, four times per week. Vascular access is achieved either through a tunneled, indwelling catheter such as a permcath or an arteriovenous fistula. During infant dialysis if the volume of the extracorporeal circuit volume is greater than 10% of the estimated total blood volume (TBV) a circuit prime with 5% albumin or blood is recommended.

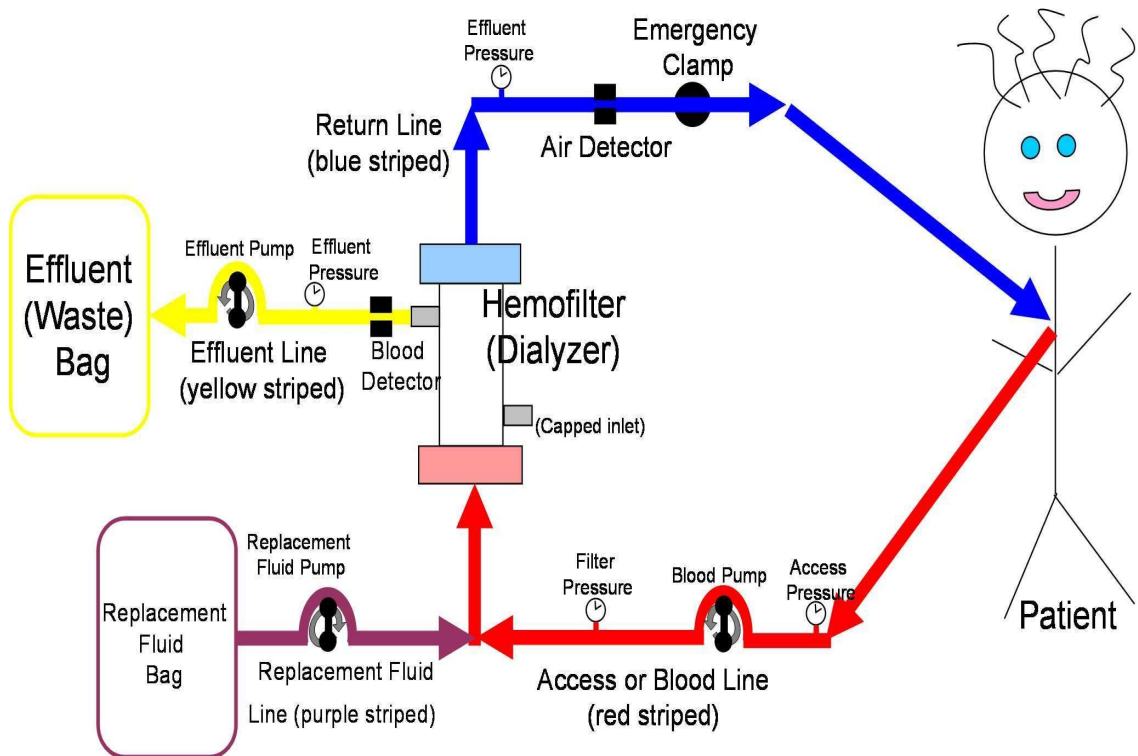


Figure 1.3: Schematic diagram of a haemodialysis circuit

With increasing blood flow, more solute is delivered to the dialyzer, resulting in higher dialyser clearance but this clearance advantage starts leveling off at blood flows of 250-300mls/min and therefore where possible a blood flow rate as close to 300mls/min is used. In children however the effective blood flow rate is largely determined by the vascular access and adjusted to achieve a 4-6mls/kg/min urea clearance, approximating a Kt/V of > 1.2 ⁴⁰, or in infants a minimum of 20mls/min to avoid the risk of clotting the circuit. The problem with small, high resistance double-lumen central venous catheters or occasionally single lumen catheters is an increased risk of high recirculation rates with inadequate dialysis on conventional dialysis regimens. This can be improved by changing the dialysis time by increasing the frequency or duration of treatment.

As a general rule to maximise effective dialyser clearance the ratio between dialysis fluid and blood flow should be at least 1.5 to 2 and in children typically dialysis flow rates of 300-500mls/min are employed, even in infants with low blood flow rates. The dialysate temperature is most commonly set at a constant temperature of 37°C. Bicarbonate is now routinely used as the acid buffer and intravenous heparin anticoagulates the extracorporeal circuit. With a desired objective of achieving long-term solute balance the dialysate sodium, magnesium, calcium and potassium composition can be adjusted in accordance with the patient's plasma levels.

1.6 Cardiovascular Response to Haemodynamic Stress

During HD both UF and plasma solute clearance induces fluid exchange that ultimately results in intravascular fluid depletion. This haemodynamic stress triggers a

characteristic compensatory response which owing to differences in physiological maturity is age dependent but is ultimately aimed at restoring circulation adequacy.

In general the cardiac output is predominantly determined by the heart's loading conditions. Preload is defined as the ventricular wall tension at the end of diastole and is largely derived from the circulating blood volume and venous capacitance. The velocity and power of contraction in single fibres is directly related to fibre length at the beginning of contraction (The Frank-Starling law). As the preload increases the stroke volume (SV) increases but there is a limit of preload reserve. Conversely, as is the case during HD, as the preload decreases the SV decreases. Afterload is the sum of forces opposing ventricular ejection and the most important component is total peripheral resistance (TPR) or systemic vascular resistance. SV decreases as afterload increases but by increasing the contractility of the heart some gain in SV can be achieved. Heart rate (HR) increases cardiac output but by reducing the time spent in diastole rapid rates can decrease SV by limiting ventricular filling and reducing coronary arteries perfusion. As SV increases the myocardial demand for oxygen rises and coronary blood flow must rise to compensate. Finally in a response to reduced cardiac output, vascular tone is increased in attempt to preserve the central blood pressure and maintain vital organ perfusion.

Ventricular compliance is also an important component of cardiac output. Ventricular filling occurs in two stages, the rapid early filling which is associated with ventricular relaxation and then the slower later filling that is augmented by atrial contraction. As ventricular compliance decreases the end-diastolic volume for a given end-diastolic pressure falls and in these circumstances the slow phase dominates. An increase in

heart rate will accelerate the rate of relaxation and may precipitate a fall in cardiac output. Similarly ischaemia compromises the rate and extent of relaxation.

Neonates at the time of birth have reduced inotropic and preload reserve and thus their dominant response to a haemodynamic challenge is tachycardia. The sympathetic innervation of the neonatal heart is less well developed than the parasympathetic and thus they have a propensity for reflex bradycardia. Compared with older children any fall in HR is accompanied by an attenuated vasoconstriction response and disproportionately larger decreases in cardiac output. Therefore as afterload increases cardiac output falls but in the reverse as the afterload falls there is a less impressive gain in output. In infancy and childhood the myocardium adapts progressively and develops an increased reserve to β adrenergic stimulation.

Stressors such as HD cause intravascular fluid depletion. As the effective circulating volume falls, the preload, SV and cardiac output would fall. In an attempt to maintain the central BP one would expect a local hormonal, metabolic and sympathetic stimulus increases vascular tone and total peripheral resistance. In the presence of arteriolar constriction the distending pressure to the vein is reduced and blood is extruded centrally towards the heart to maintain cardiac refilling.

Uraemia is associated with a maladaptive cardiovascular response but what is unknown in paediatrics is the extent to which the processes described above are abnormal.

1.7 Blood Volume Monitoring and Ultrafiltration

On-line non-invasive blood volume monitors (NIVM) make it feasible to indirectly measure blood volume, both real-time and continuously throughout dialysis. They are based on the principle of mass conservation: the concentration of measured blood constituents (haemoglobin/haematocrit/plasma protein) confined to the vascular space, change in proportion to changes in the vascular volume. It is also assumed that the total concentration of blood constituent in the circulation is constant with uniform mixing throughout the vascular space. NIVMs differ by the intrinsic sensing techniques that are used for monitoring.

Optical: measures the optical absorbance of monochromatic light, via an optoprobe in the arterial line. The optical density of whole blood is really a measure of red blood cell (RBC) concentration - the haematocrit, rather than the haemoglobin content. Scattering of light from the surface of RBC yields a non-linear relationship between the measured optical density and hematocrit. The Crit-line (In-Line Diagnostics, Riverdale, Utah), a stand alone device, is however designed to correct for this while the Hemoscan (Hospal-Dasco, Medolla, Italy) which forms part of the dialysis machine, adjusts for variations in oxygen saturation.

Blood density: blood density is dependent on the total protein concentration (plasma protein concentration + mean cellular haemoglobin concentration). The Blood Volume Monitor (BVM, Fresenius AG, Bad Homburg, Germany) measures the velocity of sound through blood, by means of a cell inserted in the pre-pump segment of the arterial line, adjusted for temperature, a factor known to impact on both sound velocity and blood density.

Electrical conductance: conductivity of blood depends on hematocrit, temperature, plasma electrolytes and non-electrolyte concentrations. The difference of high and low frequency conductivity has been found to be a measure of hematocrit. The extracorporeal plasmatic impedance meter (IPEC, Laboratoire Eugedia, Chambly, France) translates changes in conductivity into relative changes in the plasma volume.

All three devices report results as a percentage relative change of the blood volume (RBV), and in some, these are displayed graphically. Each device is fitted with computer software that converts measured changes to percentage RBV based on an internal calibration reference points. These may differ between machines and therefore an absolute RBV value on one device may not read the same on another. Schneditz et al demonstrated a 2% difference in relative blood volume changes (BVM 2% less reduction in blood volume compared to Crit-line), which developed approximately 1 hr into dialysis, and persisted thereafter ⁴¹.

NIVM measures the change in blood volume as fluid is being removed during UF and thereby provides additional insight into vascular refilling ability. Theoretically, this could guide UF rates based on observed RBV changes as demonstrated by the four relative blood volume (RBV) curves shown in Figure 1.4.

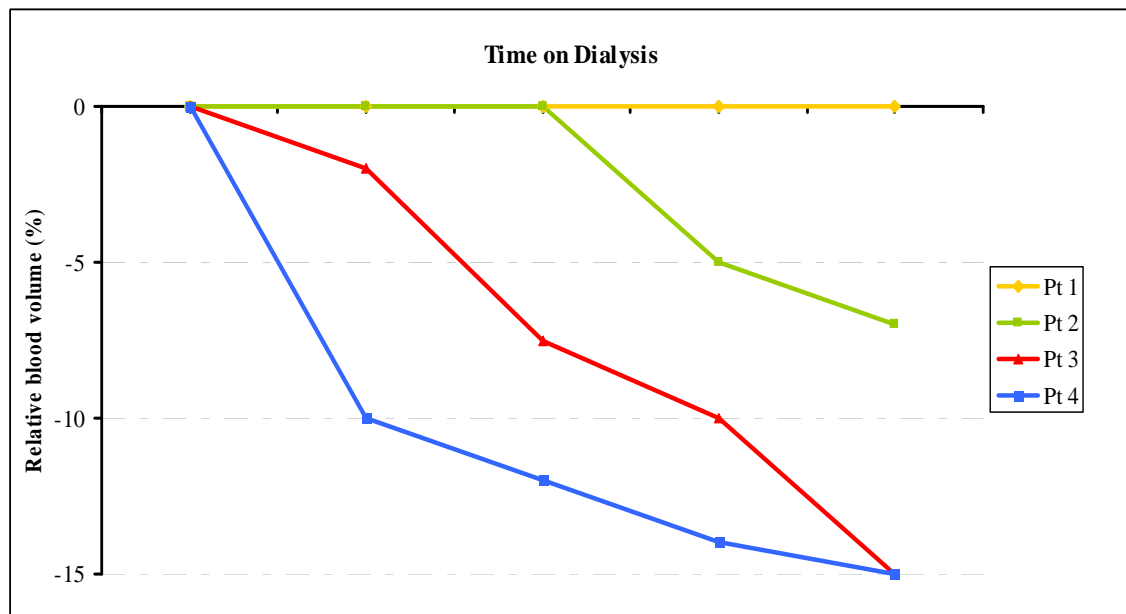


Figure 1.4: Examples of relative blood volume curves taken during haemodialysis

- *Patient 1* has a flat line throughout dialysis and hence plasma refilling rate is able to fully compensate UF rates. In fact one could assume the patient has an excess of fluid in the interstitial space as refilling rates remain high throughout dialysis. It is thus probable that the patient will tolerate higher UF rates.
- *Patient 2* has a constant RBV curve during a first part of dialysis followed by a linear decrease. This would indicate compensated UF up to the point that the curve is flat but thereafter the plasma refilling rate is not able fully compensate UF rate and thus the RBV falls.
- *Patient 3* shows a linear decrease of RBV from the onset of dialysis with a constant declining slope. In this patient the UF rate is always exceeding the plasma refilling rate and therefore if the UF rate was to be increased there is a risk of precipitating decompensation.

- *Patient 4* shows a linear decrease of RBV with a variable declining slope. In this patient fluid removal is too rapid at the onset as demonstrated by the steep decline in RBV and the risk of symptoms secondary to hypovolaemia is high. The UF rate needs to be revised to reduce intradialytic morbidity.

Steuer et al achieved a 2-fold reduction in intradialytic symptoms using NIVM in six hypotension prone adults, without changing the UF volume or treatment times⁴². Additional benefits that have been reported in adults are an increase in the UF potential, lowering of the dry weight, improved patient well-being and reduced hospitalization due to fluid overload. Access to information on blood volume status would be particularly helpful in the paediatric HD setting as the prevalence of intra- and interdialytic morbidity can be higher when children do not often verbalize early warning symptoms and for differentiating between symptoms caused by aetiologies other than hypovolaemia. Responding directly to RBV changes with RBV driven algorithms have shown decreased UF associated symptoms and antihypertensive medication burden, with the greatest impact on children weighing less than 35 kg⁴³⁻⁴⁵. Michael et al defined a safe UF rate based RBV change of < 8 % per hour in the first 90 mins and then < 4 % thereafter, with no more than a 12 % net RBV change per dialysis session⁴⁴ but there is no data on the predictability of RBV levels of impending intradialytic symptoms or hypotension in paediatrics. Adult literature has been more comprehensive and results have been conflicting. Kim initially showed⁴⁶ that if RBV fell below a given threshold, arterial hypotension appeared. Subsequently, larger observational studies demonstrated that critical maximal RBV reduction had no predictive power but found that irregularity of the RBV curve and switching from an exponential to a linear decrease were the most powerful predictors of intradialytic hypotension^{47, 48}.

1.8 Myocardial Architecture and Function

1.8.1 Myocardial Contraction

The muscle of the heart is layered in a helical arrangement with complex spatial organization of the left ventricle (LV) myocardial fibres⁴⁹. Cardiac muscle is not a homogeneous muscle mass, but shows variations at a microscopic level between individuals and further changes arise from disease states. Circumferentially oriented myocardial fibres form the largest proportion of fibres and are primarily found in the midwall layer and longitudinally oriented fibres are primarily found in the endocardial and epicardial layers⁵⁰(see figure 1.5).

Three perpendicular axes define the local myocardial fibre direction of movement: radial (*R*), circumferential (*C*), and longitudinal (*L*) as shown in Figure 1.6. The circumferential axis is tangent to the surface and oriented in the short-axis direction for both the epicardium and endocardium; the longitudinal axis is tangent to the surface and oriented in the cardiac long axis; and radial axis lies in the direction perpendicular to the wall and is tilted near the apex because of the taper of the LV.

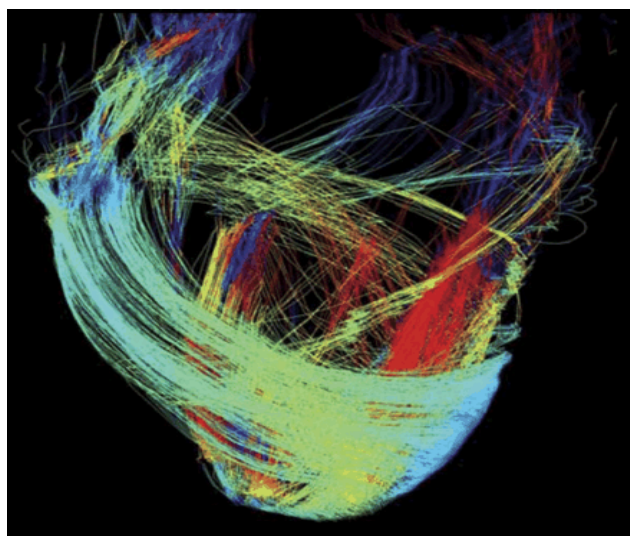


Figure 1.5: MRI reconstruction of ventricular muscle fibre orientation⁵¹

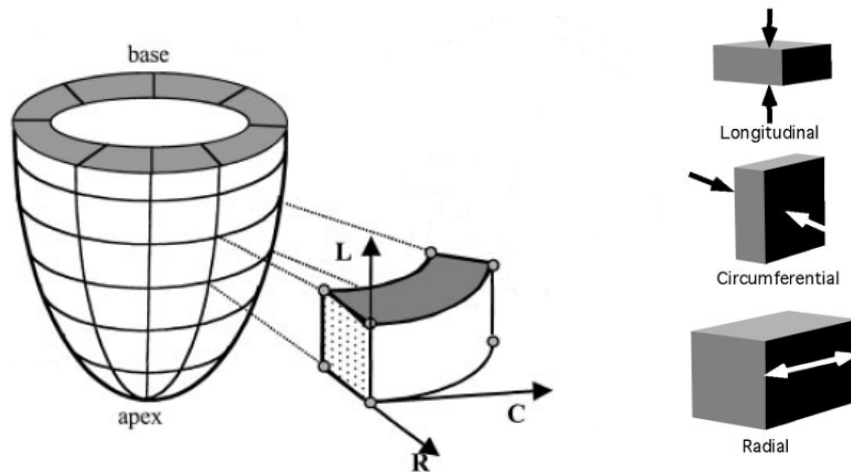


Figure 1.6: Diagram illustrating the direction of local myocardial fibre arrangement and resultant deformation ⁵²

Myocardial contraction is a complex three-dimensional motion. At the macroscopic level a combination of wall (radial) thickening, circumferential shortening, and longitudinal shortening occurs. Consequently ejection is combined effect of the inward pressure generated from concentric forces when these muscle layers start to tense and longitudinal shortening. The LV apex rotates counter clockwise (as viewed from the apex) and the base rotates clockwise creating a torsional deformation from oppositely wound epicardial and endocardial myocardial fibres. Internal cardiac fibres moved to the outside and those on the outside move to the inside. The reverse happens in diastole. The resultant effect is a twisting motion, like a wet cloth being wrung out with the apex fixed while the base of the heart ‘screws down’ onto the apex. Changes in the intracavity volume occur as a result of the inward motion and deformation (circumferentially and longitudinally) of the endocardium. Both the circumferential and longitudinal shortenings contribute to the magnitude of the ejection fraction ⁵³ but in normal individuals midwall circumferential fibre shortening appear to be the most important component.

During systolic ventricular contraction the subendocardial coronary vessels, namely the vessels that enter the myocardium, are compressed due to the high intraventricular pressures. However, the epicardial coronary vessels, the vessels that run along the outer surface of the heart, remain patent. Because of this, blood flow in the subendocardium stops. As a result most myocardial perfusion occurs during heart relaxation (diastole) when the subendocardial coronary vessels are patent and under low pressure.

1.8.2 Coronary circulation

The major vessels of the coronary circulation are the left main coronary that divides into left anterior descending and left circumflex branches, and the right main coronary artery. Both of these arteries originate from the root of the aorta, immediately behind the aortic valve leaflets, left coronary artery originates from the left aortic sinus, while the right coronary artery originates from the right aortic sinus.

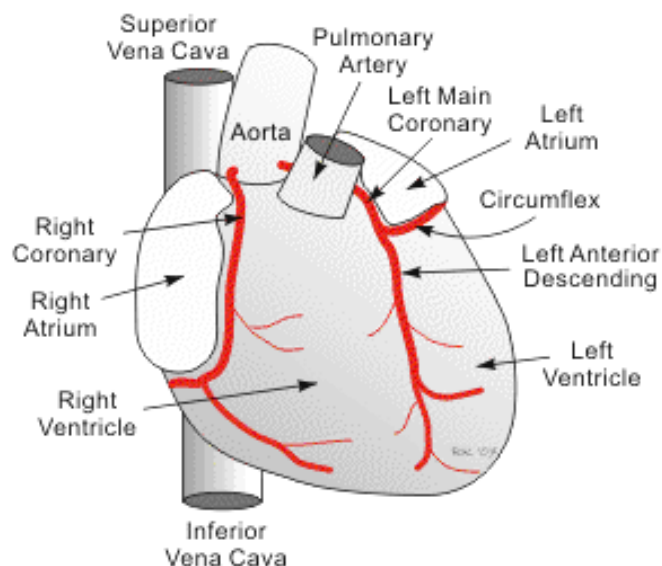


Figure 1.7: Coronary circulation

The coronary arteries sub-divide to form three compartments. Firstly the proximal compartment which constitutes the large epicardial coronary arteries. These lie on the surface of the heart, large capacitance function and offer very little resistance to coronary blood flow but are responsive to flow mediated dilatation. Their anatomical blood supply to regions of the heart is shown in Table 1.1; nonetheless the exact anatomy can vary considerably between individuals, especially in the apical cap.

Table 1.1: Anatomical blood supply to regions of the heart

Anatomic Region of Heart	Coronary Artery (most likely associated)
Inferior Infero-septal	Right coronary
Anterior Antero-septal	Left anterior descending
Infero-lateral Antero-lateral	Left circumflex

The coronary arteries then divide into pre-arterioles. These vessels maintain the pressure within a narrow range when coronary flow or intravascular pressure varies. They are essentially the principle site of autoregulation. The vessels then finally divide into intramural arterioles with diameters less than 100µm serve to ensure that myocardial blood supply adequately meets the metabolic demand of the heart. Their role is the metabolic regulation of coronary blood flow and these dilate in response to various metabolic stimuli.

The objective of the combined autoregulatory mechanisms within the coronary circulation is to match blood flow with myocardial oxygen consumption and this is done

principally by coordinating vascular tone and resistance. There is a degree of reserve within the system, the coronary flow reserve and this refers to the magnitude of the increase in coronary flow that can be achieved in going from basal coronary perfusion to maximal coronary dilatation.

1.8.3 Echocardiography

Two dimensional (2D) echocardiography use ultrasonic waves directed perpendicularly to the heart to provide real-time imaging of the heart. This also provides the means to assess cardiac function non-invasively. Global LV systolic function is usually assessed by the resting LV ejection fraction (LVEF), expressed as the ratio of the stroke volume divided by the end-diastolic volume.

$$\text{Stroke volume (SV)} = \text{LV end-diastolic volume} - \text{LV end-systolic volume}$$

$$\text{LVEF (\%)} = (\text{SV} / \text{LV end-diastolic volume}) \times 100$$

In order to assess regional LV systolic function the heart has to be divided into segments. A standardised 17 segment model recommended by The American Heart Association (AHA)⁵⁴, names segments according to their location relative to the long axis of the ventricle and 360° circumferential locations on the short-axis views as shown in Figure 1.8. In spite of the probable variability in the coronary artery blood supply to myocardial segments, a consensus has been reached on assigning the 17 myocardial segments to the territories of the left anterior descending (LAD), right coronary artery (RCA), and the left circumflex coronary artery (LCX) (see Figure 1.9) with a note of caution that the greatest variability in myocardial blood supply occurs at the apical cap, segment 17.

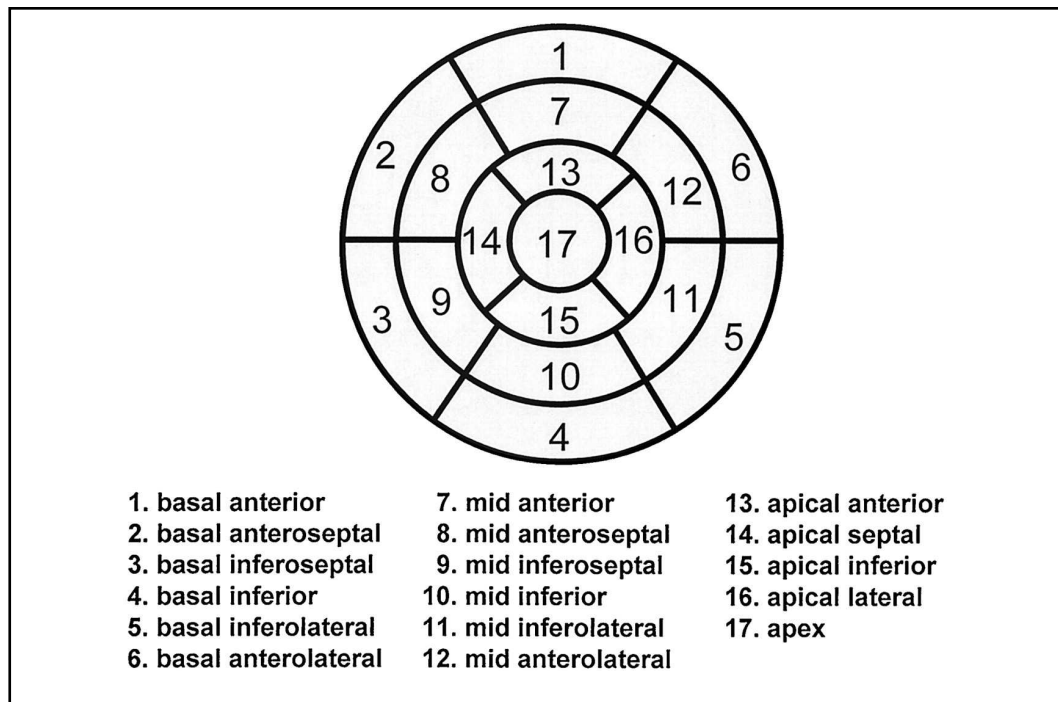


Figure 1.8: Left ventricle Segmentation⁵⁴

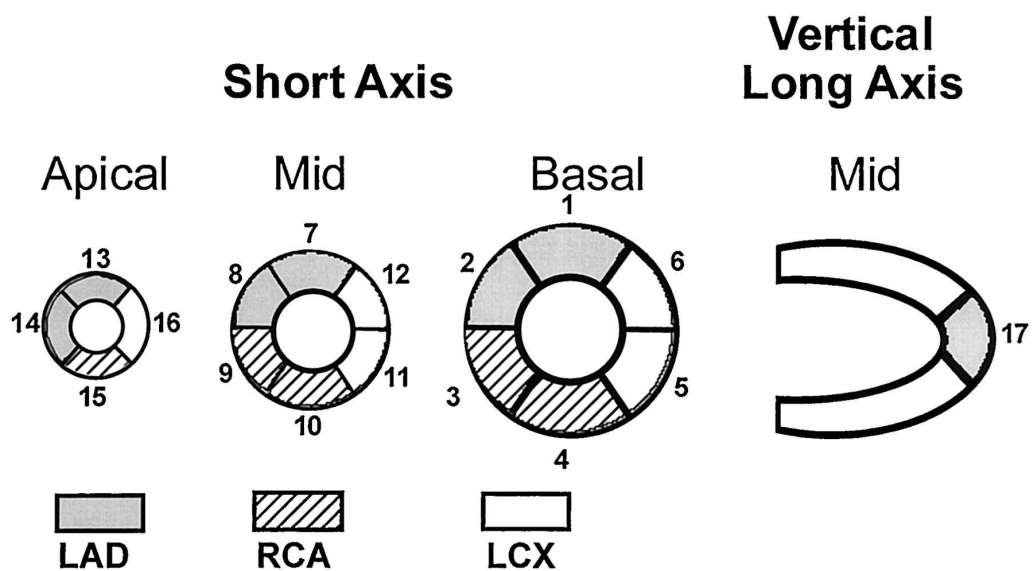


Figure 1.9: Assignment of the 17 myocardial segments to the territories of the left anterior descending (LAD), right coronary artery (RCA) and the left circumflex coronary artery (LCX). The greatest variability in myocardial blood supply occurs at the apical cap, segment 17⁵⁴.

Regional myocardial contractile function can be assessed by measuring myocardial wall motion measurements (displacement and velocity) or wall deformation (strain). The term "strain" refers to the fractional or percentage change from the original, unstressed, dimension or the change in length corrected for the original length. In common terms, deformation of a heart fibre is akin to stretching of the heart fibre. Myocardial strain is dimensionless and usually shown as a percentage. Through the assessment of segmental myocardial strain the contraction/relaxation pattern of the LV can be followed in 3 planes; longitudinal, circumferential, and radial. In comparison routine echocardiographic assessment of regional wall motion activity will only provide information on longitudinal axis function.

1.9 Myocardial Stunning

1.9.1 Definition

- Myocardial stunning is defined as transient, post-ischaemic, left ventricular dysfunction with normal or near- normal myocardial perfusion ⁵⁵
- Episodes of transient myocardial ischaemia can be followed by reversible left ventricular (LV) dysfunction, namely reduced or absent contraction in global or discrete parts of the LV

1.9.2 Evidence for haemodialysis induced myocardial stunning

In order to establish whether HD induces myocardial stunning three criteria needed to fulfilled, intradialytic i) myocardial ischaemic injury, ii) reduced myocardial blood flow and iii) segmental or global LV dysfunction. I present the evidence for all three of these criteria in adult HD patients.

Short intermittent HD treatments cause significant hypovolaemia and intradialytic hypotension (IDH)^{56, 57}. Acute rise of cardiac troponin-T (cTnT) levels following dialysis has been speculated to indicate subclinical myocardial cell injury^{58, 59}. This parallels several studies demonstrating silent ST segment depression during dialysis at rates that vary between 15 and 40%⁶⁰. In addition to cTnT, brain natriuretic peptide (BNP) is gaining increasing recognition as a marker of acute myocardial cell damage. There is evidence that a combination of elevated BNP, in combination with elevated markers of inflammation such as interleukin 6 (IL-6), predicts stunned myocardium, whereas elevated BNP with normal IL-6 levels correlate with non-viable, infarcted myocardium⁶¹. In addition, elevated BNP levels predict mortality in dialysis patients⁶². Elevated biomarkers of myocardial damage have also been demonstrated in children with chronic kidney disease⁶³.

Although there was initial debate as to whether these biochemical and electrocardiographic abnormalities reflect silent ischaemia or changes in electrolyte concentrations, subsequent studies measuring myocardial blood flow strengthen the case for ischaemia. Using single photon emission computed tomography dialysis induced perfusion defects have been demonstrated⁶⁴. In a small cohort of patients with and without large vessel epicardial coronary disease, regional myocardial blood flow fell. The segments demonstrating, transient, intradialytic LV dysfunction also exhibited the greatest reduction in regional myocardial blood flow. The duration of LV dysfunction extended beyond the period of reduced perfusion and was thus more in keeping with myocardial stunning than stress cardiomyopathy (see Figure 1.10 and 1.11).

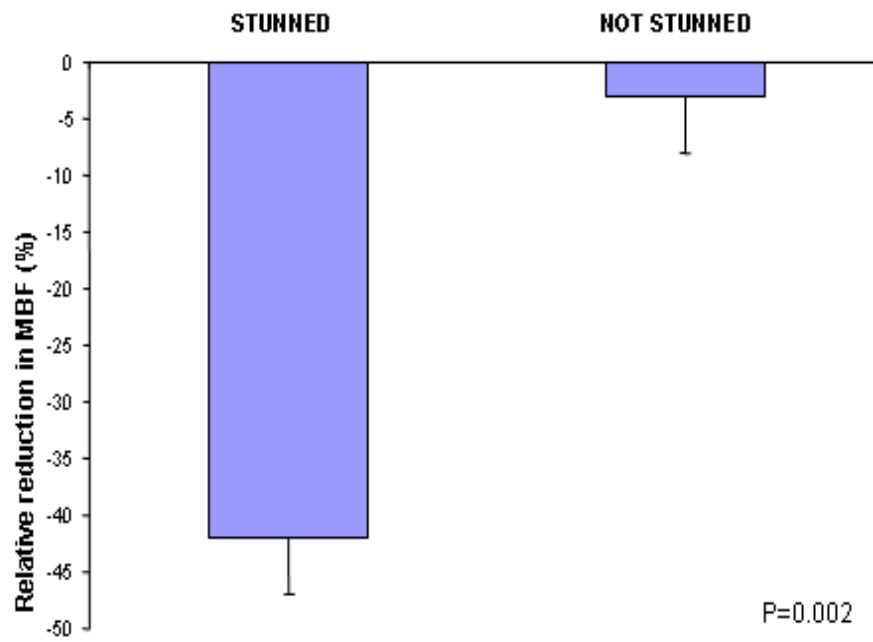


Figure 1.10: HD is associated with both reduced global and segmental myocardial blood flow (MBF) ⁶⁵

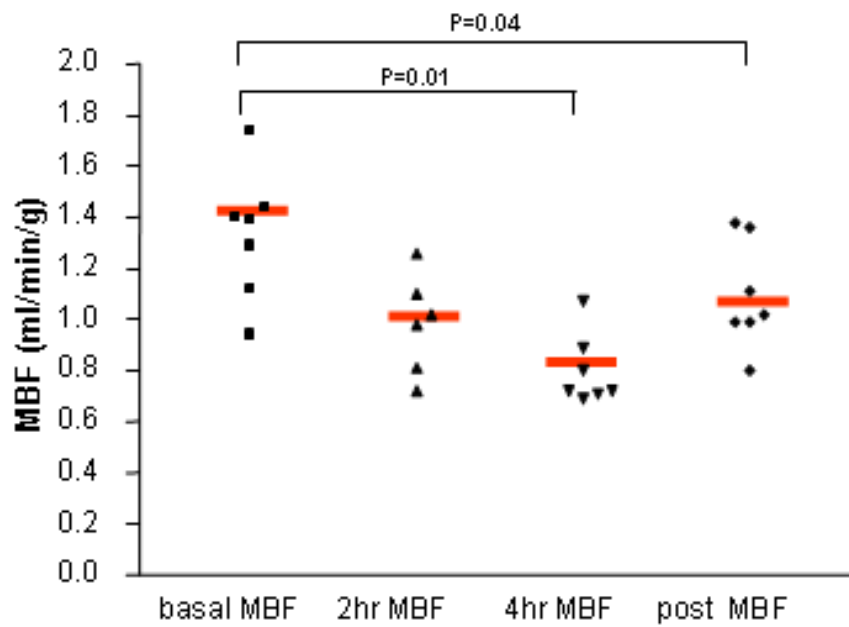


Figure 1.11 Stunned myocardial segments exhibit significantly greater reduction in myocardial blood flow (MBF) ⁶⁵

One method of examining regional LV function is through echocardiographic assessment for the development of new LV regional wall motion abnormalities (RWMA). New RWMA are indicative of ischaemia and their onset precedes symptoms and electrocardiographic changes. These principles form the basis and rationale for dobutamine stress echocardiography⁶⁶. In 75% of prevalent adult HD patients new RWMA have been demonstrated, starting 2 hours into dialysis, peaking at the time of maximum stress at the end of dialysis, with 30% persisting 30 minutes postdialysis. A direct correlation is seen between both the number and intensity of stunning within segments and intradialytic BP changes and UF volume⁶⁷. A study of sequential positron emission tomography (PET) scans of adult during their HD treatment reported a 13% reduction in global myocardial blood flow 30 minutes into HD, a period of minimal UF. This was accompanied by a 5% fall in cardiac output but no change in systolic and diastolic BP or heart rate was observed. By 220 minutes the global myocardial blood flow had fallen on average by 26% with a corresponding 21% drop in cardiac output, a significant tachycardic response but again a non-significant fall in systolic and diastolic BP. The regions of the heart that demonstrated the greatest segmental decline in myocardial blood flow developed new LV RWMA by the end of dialysis (see Figure 1.12)⁶⁸.

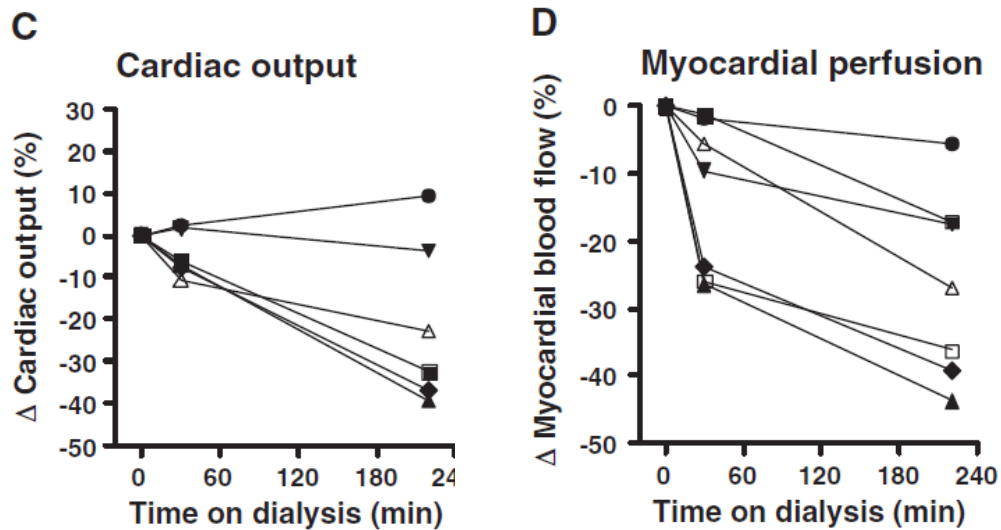


Figure 1.12: Relative change from baseline of the cardiac output (C) and myocardial blood flow (D) during haemodialysis⁶⁸

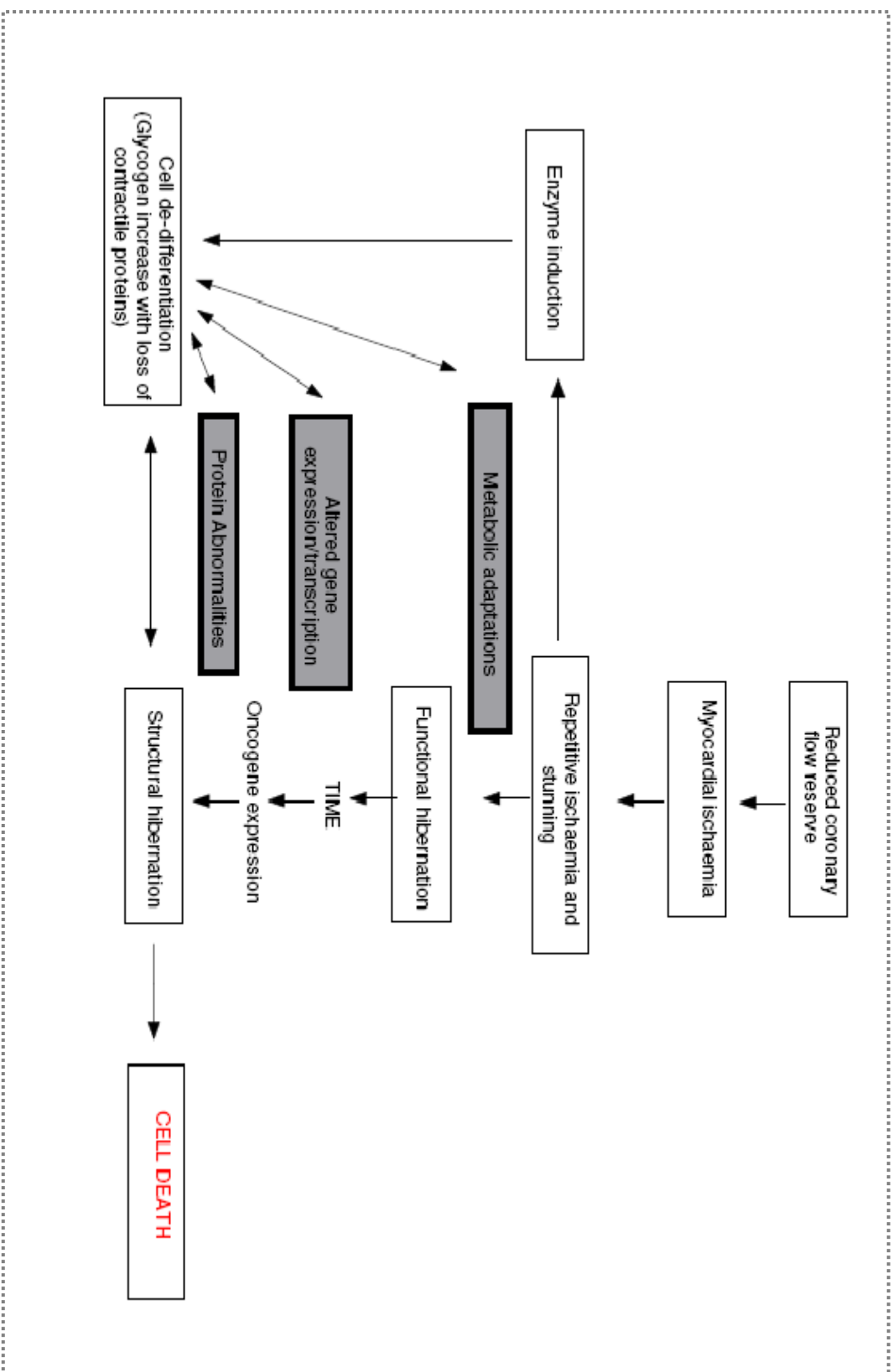
This study illustrates a pronounced fall in myocardial blood flow that occurs early during the dialysis session, unrelated to hypovolaemia and is therefore more likely to be due to a sequence of events that follow connection to the extracorporeal circuit. In patients commencing continuous renal replacement therapy, blood dialyser membrane incompatibility triggers a bradykinin response with resultant early onset hypotension⁶⁹. A similar inflammatory reaction is possible in the conventional HD patients however this alone does not explain the predominance of myocardial haemodynamic changes but raises suspicion about the integrity of myocardial microcirculation. This study also demonstrated that the reversible regional left ventricular dysfunction lasted beyond the period of reduced perfusion. This in essence completes the clinical evidence for HD induced myocardial stunning in adults.

Consequences of myocardial stunning

The concept of myocardial stunning was first introduced in patients with ischaemic heart disease. Repeated episodes of ischaemia and stunning may lead to cumulative, more severe and prolonged stunning⁷⁰ eventually progressing to the phenomenon of ‘myocardial functional hibernation’, that is non-infarcted, scar free myocardium with fixed systolic dysfunction ranging from hypokinesia (depressed contraction), akinesia (no contraction) or dyskinesia (paradoxical contraction)⁷¹. The extent and severity of LV dysfunction can vary considerably and untreated is predictive of morbidity. If a discrete region of the LV is involved the impact on ejection fraction can be minimal, however with more global involvement heart failure is inevitable.

Myocardial hibernation is thought to represent a functional adaptation to chronic hypoperfusion with cardiac myocytes almost adopting an embryonic phenotype⁷². There is conflicting evidence on whether myocardial blood flow to hibernating myocardium is normal^{72, 73} or reduced⁷⁴ but what is clear is that the coronary flow reserve is severely reduced⁷⁵. Importantly the chronic LV dysfunction that is typical in hibernating myocardium can be reversed with restoration of regional myocardial blood flow⁷⁶. If this fails to occur the hibernating myocardium is highly vulnerable to increases in demand or reductions in oxygen supply and subsequent stresses are cumulative. The knock on effect is a prolonged period to recovery following revascularisation or eventual apoptosis or necrosis and non-viable myocardium (see Figure 1.13).

Figure 1.13: Repeated episodes of transient myocardial ischaemia lead to maladaptive intracellular changes



In adults the physiological strain and haemodynamic stress during conventional HD is sufficient to cause transient myocardial ischaemia with resultant left ventricular (LV) dysfunction. Conventional HD regimens comprise of 3 to 4 dialysis treatments per week, every week of the year, therefore the potential for repetitive ischaemic myocardial insults is both significant and high. Burton et al have undertaken serial echocardiographic assessments of global and regional LV performance in prevalent HD patients, twelve months apart. They found a significant reduction in segmental shortening fraction SF in those segments that had developed RWMA's at baseline (Figure 1.14) with 32% developing a fixed reduction in segmental function.

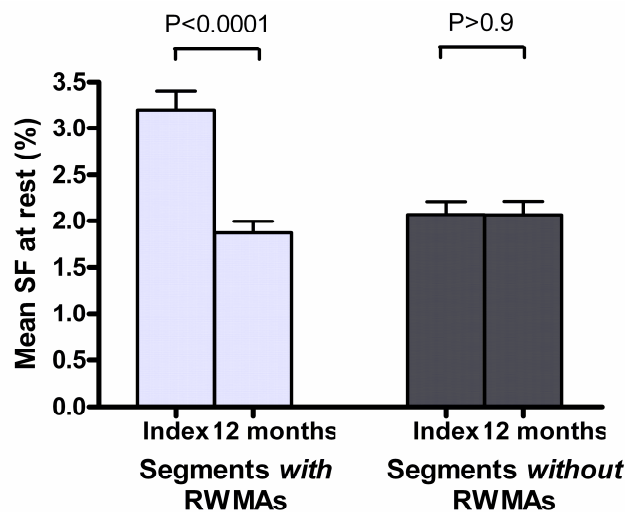


Figure 1.14: Change in segmental shortening fraction (SF) in haemodialysis patients followed for 12 months⁶⁷

Furthermore patients segments with fixed systolic reduction of >60% showed a significant decline in ejection fraction over 12 months both at rest and at peak stress during HD. There was no significant reduction in LVEF in patients who did not develop fixed reductions in segmental function (Figure 1.15)⁶⁷.

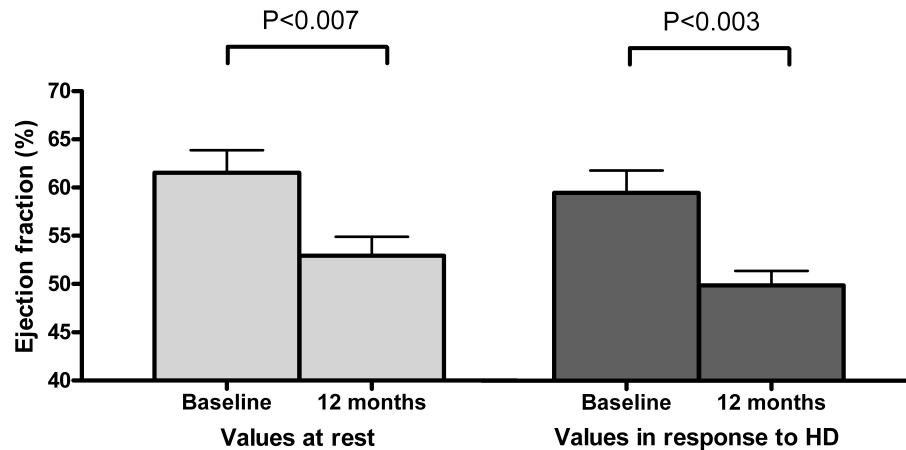


Figure 1.15: Change in ejection fraction (EF) at rest and during HD in patients with a fixed reduction in segmental function greater than 60% ⁶⁷

Records from the US Renal Data System have shown that HD is an independent risk factor for the development of both de novo and recurrent heart failure with a two-year mortality after a diagnosis of congestive heart failure as high as 51% ⁷⁷. The aetiology of uraemic heart failure is elusive but evidence implicating HD induced myocardial stunning story is emerging. However what remains uncertain is whether children on HD are also vulnerable.

1.10 Strategies for improving intradialytic morbidity

1.10.1 Sodium profiling

Following a sodium load, the mechanisms responsible for preserving plasma tonicity will maintain plasma sodium within narrow limits by changing the plasma volume. During HD, dialysate sodium generates a crystalloid osmotic pressure and thus influences fluid shift between the different body compartments, but it also permeates the dialysis membrane and thus has the potential for becoming a sodium load.

One of the primary objectives of HD is restoration of sodium and fluid balance. Sodium is predominantly cleared by convection with the excess water. Pure UF has approximately the same sodium activity as plasma with no net change in patient's plasma sodium concentration. Diffusive sodium transport is proportional to the difference in sodium concentration between blood and dialysate compartments. Dialysate sodium activity is approximately equal to 97% of the measured sodium concentration. Similarly the proportion of plasma sodium ions that are bound to protein and other anions, are unavailable for exchange. We can measure the free ionized plasma water sodium concentration in the blood by using direct ionometry. Plasma sodium activity is further limited by the Donnan effect, whereby negatively charged proteins (mainly albumin) produce a small electrical potential difference across the membrane (negative on the plasma side) that prevents movement of the positively charged sodium ions. Concentration differences between interstitial and plasma also stem from the Donnan effect. In the absence of UF, we can approximate the concentration of dialysate sodium to achieve isotonic dialysis by correcting the blood sodium measured by direct ionometry for a Donnan factor of 0.967.

Hyponatric dialysis causes osmotic fluid shift from the extracellular to intracellular compartment, dialysis disequilibrium disorder and intradialytic hypotension. Hypernatric dialysis transfers sodium to the patient, causing interstitial oedema, interdialytic thirst, increased interdialytic weight gain and the worsening hypertension. A therapeutic advantage can be gained by manipulating the dialysate sodium concentration throughout dialysis. This is referred to sodium profiling, and typically utilizes a sodium concentration that falls in a step, linear or exponential fashion. The higher dialysate sodium at the start allows a diffusive sodium influx to counterbalance

the rapid decline in plasma osmolality due to clearance of urea and other small molecular weight solutes. Low dialysate sodium at the end aids diffusive clearance of the sodium load and minimizes hypertonicity. Compared with a constant dialysate sodium bath modelling has been shown to increase stability of intradialytic blood volume, and reduce both intradialytic cramps and interdialytic fatigue in adults and children⁷⁸. Outcomes have been better with the linear and step profiles compared with exponential. Step profiles are most effective at attenuating post-dialytic hypotension and early intradialytic hypotension and linear profiles best reduced cramps and late intradialytic hypotension. Sodium profiling is also indicated in the prevention of dialysis dysequilibrium with patients reporting a preference to it. However one of the major drawbacks of sodium profiling is the risk of a positive sodium balance by the end of each HD session.

The challenge therefore with sodium profiling is finding the concentration gradient that offers the benefits of cardiovascular stability without exposing the patient to a small but repeated sodium load. A net sodium gain of 1mmol/l will result in a 1.3% expansion of the extracellular space. Based on concerns of inducing hypervolaemia the emphasis is shifting to neutral sodium balance profiles. Protocols of isonatremic dialysate are similar with time averaged dialysate sodium 2-3mEq/l lower (Donnan effect) than the predialysis sodium⁷⁹. Results indicate benefits comparable to sodium profiling with a significant decrease in the interdialytic weight gain and thirst score⁸⁰.

Currently the decision to manipulate dialysate sodium relies heavily on conflicting adult literature and there is no comparison of its benefit over other commonly used strategies such as UF profiling in children.

1.10.2 UF profiling

Modifying the UF rate throughout dialysis to allow adequate vascular refilling has the potential to increase the UF potential. This is the rationale behind UF profiles. The plasma refilling capacity increases proportionately with interstitial volume expansion. Decreasing stepwise or linear profiles start with high UF rates at the time of maximal tissue hydration, progressively reducing the rate in line with decreasing interstitial hydration in the hope of maintaining the crucial balance between fluid removal and vascular refilling. Intermittent profiles aim to provide periods of active mobilization of interstitial fluid into the vascular space when UF rates are low, thereby making it amenable to removal during periods of high UF rates. Donauer et al reported lower symptomatic hypotension with the decreasing profiles, but the intermittent profile was associated with an increased incidence of symptomatic hypotension and post-dialysis fatigue⁸¹. The incidence of intradialytic hypotension was highest with UF rates greater than 1.5 times the average. Ronco et al observed hypotension at a rate of 6.7/100 treatments when the UF rate was 0.3 ml/min/kg increasing to 15.8 at an UF rate of 0.4 ml/min/kg, 25.6 at a rate of 0.5 ml/min/kg, and 67.4 at a rate of 0.6 ml/min/kg⁸².

Combining UF profiles with sodium profiles can induce plasma hypertonicity. The utilisation of a high UF rate with higher dialysate sodium conditions maximises plasma refilling and in adults has been shown to be superior to either sodium or UF profiles alone in attenuating intradialytic symptoms and cardiovascular instability. Ebel et al compared 3 regimens; i) constant dialysate sodium of 138mmol/l, ii) UF profile of 40% of the total UF goal in the first hour, 30% in the second hour, 30% in the subsequent 90mins and then none in the last 30mins, iii) combined UF profile with a sodium profile with a dialysate sodium 10% higher than the pre-dialysis plasma sodium, decreased in 5

steps to 138 in the last hour. Both the stand alone UF and sodium profiles showed evidence of intracellular fluid shift and intravascular hypovolaemia. The combined profiles showed higher refilling rates and net removal of fluid from the interstitium and reduced renin, aldosterone, epinephrine and norepinephrine levels⁸³, perhaps reflecting less marked hypovolaemia and improved vascular stability. Paediatric data on the use of UF profiles in isolation or in combination with sodium profiles is non-existent and thus efficacy large extrapolated from adult data.

1.10.3 Biofeedback

The kidneys' unique ability to maintain homeostasis is achieved by continuously adjusting purification in response to transfer of information through a complex system of sensing and feedback mechanisms. Until now we have been unable to simulate this because traditional HD prescriptions are based on information from previous observations. Recently introduced biofeedback systems adjust the treatment prescription based on real-time repeated observations from an on-line monitoring system using a negative feedback system designed to return the deviating factor to a pre-set nominal value.

Blood volume controlled feedback systems respond to RBV changes⁸⁴. At the start of therapy the treatment duration, UF goal, and a target for a maximum decline in BV is set. The feedback programme will then adjust the UF rate and (when using the Hemocontrol module) dialysate conductivity to maintain RBV along this pre-set target thus improving RBV preservation with a more physiological reduction in the RBV profile^{85, 86}. Initial results report a reduced incidence of intra-dialytic hypotensive episodes and attenuation of post dialysis symptoms⁸⁷ with a partial response in

hypotension prone patients^{84, 88}. Again data in paediatrics is non-existent, nevertheless RBV driven UF algorithms have been used in children with success with reports of reduce antihypertensive medication burden and UF associated symptoms⁸⁹.

1.10.4 Sequential dialysis

Owing to anecdotal experience iso-osmotic fluid removal during sequential dialysis techniques (pure UF followed by dialysis) is often used to achieve higher UF rates without inducing hemodynamic instability but what remains unclear is how this improvement in cardiovascular stability is achieved and the extent of the benefit. Isolated UF can be performed by placing the HD machine in bypass or on the UF mode. As the patient is no longer being warmed by the dialysate their core temperature drops. Traditional thinking believed this to be problematic as patients developed symptoms related to cold. In light of emerging evidence the reverse is now believed to be true. Cooling over the extracorporeal circuit counteracts the heat generated during dialysis and thus prevents an increase in core temperature, peripheral vasodilatation and hypotension. Others have postulated that the improved hemodynamic stability is secondary to decreased sodium clearance^{90, 91}. Based on personal experiences there is no doubt that sequential dialysis can be useful in meeting UF targets during paediatric HD but quantitative, comparative data has never been reported.

1.10.5 Intradialytic mannitol

Dialysis discomfort and dysequilibrium due to cellular osmotic distress occurs as a result of changes in osmolarity inducing water shifts from the extracellular to the intracellular compartment across the highly permeable blood brain membrane. It was first described in 1962 and manifests during or immediately after HD as a self limiting

entity but recovery can take several days. Symptoms typically include nausea, vomiting, headache, blurred vision, hypertension, seizures and coma but others such as muscular cramps, anorexia, restlessness and dizziness have been reported.

The exact pathophysiology of DDS remains unclear and two mechanisms have been proposed. The first, the reverse urea effect, believes that urea clearance from plasma occurs more rapidly than brain tissue. This results in a transient osmotic gradient and net movement of water from plasma to brain causing cerebral oedema and occasionally due to loss of extracellular water, hypotension. The second theory relates to intracerebral acidosis and emerged from evidence pertaining to a paradoxical acidemia of CSF and cerebral cortical grey matter in patients and animals treated with rapid HD. This is accompanied by increased brain osmole activity due to displacement of sodium and potassium ions and enhanced organic acid production. The increased intracellular osmolarity induces fluid shifts with subsequent cytotoxic oedema. Both mechanisms allude to rapid changes in brain volume. This in turn is thought to damage the blood brain barrier and disrupt cerebral autoregulation. Patients identified as high risk of developing DDS are new patients, those with a high pre-dialysis urea or high UF goal, children and patients with co-morbidities such as pre-existing neurological disease, hyponatraemia, malignant hypertension and hypoglycaemia.

Treatment options are both preventative and therapeutic. The dialysis prescription can be adjusted to reduce the rate of plasma urea clearance by downgrading the surface area of the dialyser; decreasing the blood flow rate; minimized intradialytic fluid shifts with sodium profiles or higher dialysate sodium concentrations and if the patient is grossly fluid overloaded to treat using sequential HD with a initial period of UF alone followed

by conventional dialysis. In paediatrics mannitol is used almost exclusively as a preventative and therapeutic agent. It is osmotically active solute, and can therefore artificially increase plasma osmolarity at the time of rapid urea clearance. Therapeutically it rapidly lowers intracranial hypertension within minutes of administration, with a maximal effect at 20-40mins. Mannitol accumulates in renal failure (half-life: 36hrs) and therefore a maximal intradialytic dose of 1g/kg is recommended.

One of the greatest challenges relating to DDS resides in the fact that the diagnosis is essentially one of exclusion, the main differential diagnosis being intravascular fluid depletion. In practice DDS is only treated when symptoms are typical and/or severe and therefore the true incidence in children is unknown. Similar to sequential dialysis the value of intradialytic mannitol in children has never been quantified, especially within the context of modifying the UF potential.

1.10.6 Cooling

By modifying skin blood flow we can control heat exchange between the body and the environment. This is mediated by two sympathetic nervous systems, an adrenergic vasoconstrictor and a less well understood sympathetic vasodilator. During times of increased body core temperature, tonic sympathetic vasoconstriction is relaxed and active vasodilatation is initiated⁹² and with heat stress the skin blood flow rate can increase from a baseline of 200-500mls/min (5-10% of the total body cardiac output) to 8l/min (approximately 60% of cardiac output)^{93, 94}.

Traditionally dialysate temperatures have been set around 37°C based on presumed physiological normal values and to compensate for losses of heat in the extracorporeal circuit. Both of these assumptions have in fact been found to be untrue. In a study of HD patients 62.5% of 128 HD adult patients had pre-dialysis body temp below 36.5, with marked inter- and intra-individual differences⁹⁵. There is growing evidence in both in adults and children of a net gain and not loss of heat during dialysis speculated to have a multifactorial aetiology. Firstly transfer of heat to patients from the warmer dialysate. As a result of a higher resting energy expenditure in HD patients compared to the normal population, especially in those with residual renal function⁹⁶. Thermogenesis as direct consequence of the inflammatory response invoked when blood comes in contact with bioincompatible dialysis membranes. Finally UF activates increased sympathetic vasoconstriction, reducing skin blood flow and therefore heat exchange, demonstrated by a direct correlation between UF volume and net heat gain⁹⁷. If the accumulation of heat causes an increase in the body core temperature, UF induced vasoconstriction is overridden by active vasodilatation. Blood is redistributed to the skin⁹⁸, the peripheral vascular resistance falls, causing decreased cardiac refilling and hypotension⁹⁹. Fine and Penner⁹⁵ showed that dialysis patients with subnormal body temperature (below 36°C) dialyzed against a 37°C dialysate had a 15.9% incidence of symptomatic hypotensive episodes, which fell to 3.4% with 35°C dialysate. Selby et al reported an improvement in the degree and severity of HD induced myocardial stunning in patients treated with cooled dialysate¹⁰⁰. This hemodynamic advantage of “cool” HD comes at a price with symptoms related to feeling cold and a theoretical risk of adversely affecting urea clearance as a result of compartmental dysequilibrium. The application of ‘cooling’ can complex using a feedback control circuit or simple through the manipulation of the dialysate temperature based on the patient’s pre-dialysis

temperature. In adults cooling has been associated with improved cardiovascular stability and reduced HD induced LV dysfunction¹⁰⁰.

1.10.7 Quotidian haemodialysis

Conversion to frequent HD has been shown to reduce intra- and interdialytic hemodynamic instability. This may simply be the result of gentler and more gradual fluid. However, there is growing evidence indicating an improvement in a number of uraemic cardiovascular co-morbidities in association with superior toxin clearance. Quotidian dialysis improves EPO responsiveness and dialysis related inflammation³⁷; hypertension and LVH^{101, 102}; conduit artery stiffness and total peripheral resistance; endothelium-dependent vasodilatation¹⁰²; and baroreflex regulation of heart rate¹⁰³.

Almost exclusively the reported literature features adult studies and paediatric data is almost exclusively gained from case series reports. In spite of this the collective experience has been positive with improved UF potential and dialysis quality and a reduction in intradialytic symptoms. One feature that is relevant in light of the work of this MD is that children converting to frequent, 8-10 hour dialysis treatments develop chronic asymptomatic pre- and post-dialysis hypotension¹⁰⁴. Again owing to a paucity of data we do not know whether this has serious implications in the short-term or in the future.

Chapter Two

Hypotheses

Nature of the Studies

Cardiovascular disease is prevalent and the most common cause of mortality in children with ESRD. Intradialytic hypotension is prevalent and in adults is a known risk factor for death. This raises a very valid question, are the two linked? The evidence for the cardiovascular burden of HD is growing stronger and with it the urgency for change in the way we dialyse our patients. The difficulty in paediatrics is the paucity of data to direct us. Studies examining the cardiovascular response to dialysis have been in adults and extrapolated to children. There is anecdotal evidence of haemodialysis induced haemodynamic disturbance and decompensation in children but the risk has not been quantified. Young adults have a constellation of ischaemia predisposing factors including increased intima media thickness and pulse wave velocity, coronary artery and valvular calcification, endothelial dysfunction and early atherosclerosis. It is therefore plausible that children may also display a similar pathophysiology of dialysis induced cardiac injury as adults.

Objectives

The objectives of this thesis are as follows:

- To determine the prevalence of intradialytic hypotension during conventional paediatric HD treatments.
- To investigate the haemodynamic response to HD in children
- To ascertain whether changes in intravascular volume are predictive of intradialytic hypotension during paediatric HD
- To investigate global and segmental myocardial function during conventional paediatric HD treatments

- To determine the efficacy of sodium and UF profiles, sequential dialysis and intradialytic mannitol in attenuating intradialytic symptoms and hypotension.

Original Hypotheses

- The aetiology of intradialytic hypotension in children is due to variations in the compensatory haemodynamic response to intravascular volume changes during dialysis. The aetiology is multifactorial and not exclusively due to UF induced hypovolaemia.
- Children with ESRD have developed significant cardiovascular disease that predisposes them to ischaemic injury. Conventional HD constitutes a significant haemodynamic stress and as such is a procedure associated with a high metabolic demand. In the presence of repeated episodes of intradialytic hypotension the resultant demand supply mismatch causes ischaemic myocardial injury and LV dysfunction.
- Through a better understanding of the mechanism involved in intradialytic hypotension the dialysis prescription can be modified to improve cardiovascular stability and intradialytic morbidity.

Chapter Three

Haemodynamic Response to Paediatric Haemodialysis

3.1 Hypotheses

- UF is associated with intravascular fluid depletion.
- Intravascular hypovolaemia induces a compensatory cardiovascular response to maintain and support adequate circulation for vital organs. During paediatric HD the dominant response varies between patients.
- Decompensation is prevented by mounting a tachycardia response, increasing cardiac contractility and stroke volume (SV) while the total peripheral resistance (TPR) rises to sustain central BP.
- Intradialytic hypotension occurs when these compensatory mechanisms fail combined with changes in intravascular volume.
- Temporal changes in relative blood volume (RBV) are not able to predict the development of intradialytic symptoms and hypotension in children but thresholds can help to discriminate between successful treatments and in those in which an adverse event occurs.

3.2 Introduction

Adults with ESRD have an altered and abnormal hemodynamic stress response^{12, 105, 106} and we assume the same to be true in children. In spite of this, with a desired objective of maintaining euvolemia we attempt to remove large volumes of fluid during conventional 4 hour HD treatments. In paediatrics, UF volumes of up to 6% of the dry weight are prescribed and achieved but at the expense of inducing intradialytic symptoms and hypotension. The aetiology of intradialytic hypotension is complex and thought to be caused in part by an impaired cardiovascular compensatory response to fluid removal, although the precise mechanisms are still not entirely understood. Plasma

refilling is thought to be an important mediator and an imbalance between UF and plasma refilling rates will eventually lead to hypovolaemia.

The introduction of non-invasive blood volume monitors (NIVM) has now made it possible to measure the relative changes in the blood volume real-time and repeatedly during individual dialysis treatments. In addition it has been suggested that RBV parameters may predict the occurrence of adverse intradialytic events. In adults a critical level of RBV reduction⁴⁶, gradient of the RBV curve or switching from an exponential to a linear RBV reduction have demonstrated predictive ability for the occurrence of intradialytic hypotension^{46, 48}. In children RBV literature is dominated by studies reporting on the merits of RBV algorithms in guiding UF^{43, 89} but the predictive and discriminating ability of RBV parameters have not been investigated.

3.3 Subjects & Methods

3.3.1 Non-invasive continuous haemodynamic monitoring

Technique

The finometer (Finapres Medical Systems, Arnhem, The Netherlands) is a tool designed for measuring BP and haemodynamic variables non-invasively, using continuous pulse-wave analysis at the digital artery (Figure 3.1). Finger arterial pressure is measured using the finger-clamp method whereby changes in digital arterial diameter are detected by infrared photoplethysmograph¹⁰⁷ and opposed by an ultra-fast pressure servo controller that changes pressure in an inflatable air bladder, both mounted in a finger cuff. This generates an arterial waveform on a beat-to-beat basis form which is then

used to reconstruct a central aortic flow waveform¹⁰⁸ and calculate a number of haemodynamic variables on a continuous basis (see Figure 3.2).



Figure 3.1: Non-invasive continuous haemodynamic monitoring with the finometer

Using a nonlinear, self-adaptive, three-element Windkessel model of aortic input impedance an algorithm computes the aortic flow waveform from an arterial blood pressure pulsation. Z_0 is characteristic impedance of the proximal aorta; C_w 'Windkessel' the compliance of the arterial system; and R_p , total systemic peripheral resistance. The input is $P(t)$, the arterial pressure waveform and output $Q(t)$ blood flow as a function of time.

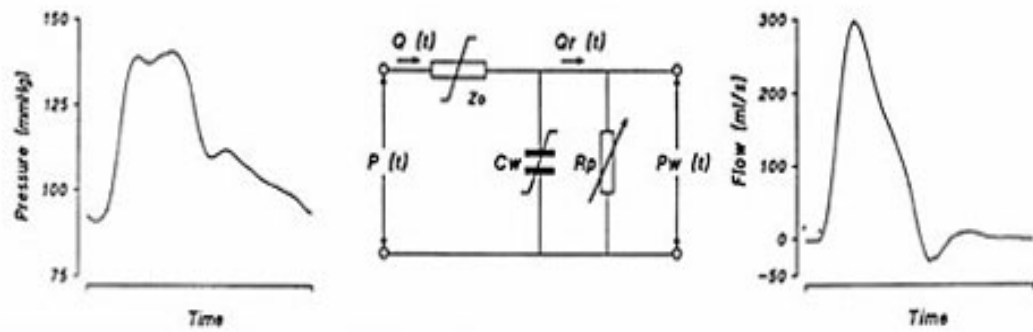


Figure 3.2: Modelling flow from measurements of arterial pressure.

Left panel: input- the non-invasive pressure for one heartbeat.

Middle panel: three-element model of aortic input impedance that is used to compute flow from pressure *Right panel:* output- aortic flow as a function of time

An arm cuff is wrapped around the same arm as the finger cuff to undertake a “Return-to-flow” calibration¹⁰⁹. When arm cuff pressure is supra-systolic, no pulsations can be sensed in the finger. The first slight pulsation signals return to flow and is sensed in the finger and detected by the software. The finger cuff pressure is read at that instant and calibrated against brachial readings. The Finometer has been validated against invasive haemodynamic measurements in both children and adults¹¹⁰⁻¹¹⁴ and shown to be accurate, reliable and reproducible.

Patients & Method

I prospectively selected all chronic HD patients treated at Great Ormond Street Hospital for Children, excluding those with overt cardiac disease. Ethics approval for this study was granted by the local research ethics board and informed consent was obtained from patients or their guardians.

The children aged from 11 to 17 years, had been dialysis dependent for 4-130 months. The net UF volume ranged from 5 to 61mls/kg. Using the finometer I measured the heart rate (HR), blood pressure (BP), stroke volume (SV), cardiac output (CO) and peripheral resistance (TPR) for the duration of the dialysis session. All the data was downloaded to a PC based analysis program to calculate average results over 5 minute time intervals.

Dialysis Prescription

All patients were dialysed using Gambro AK 95® or Gambro AK100® dialysis monitors. Patients received HD for 4 hours, 3 times per week. All dialysis membranes were high flux polysulfone or triacetate cellulose membranes, sized to match each patient's body surface area. For all treatments, dialysate contained sodium 140 mmol/l, potassium 2mmol/l, calcium 1.75mmol/l, magnesium 0.5mmol/l, bicarbonate 34mmol/l with a small quantity of acetate in the acidic component to stabilise the dialysate. The dialysate solute concentrations were not formally analysed and verified but assumed to be correct based on the from the manufacturers labels. The dialysate temperatures were set at constant value of 37.0°C. Dialysate flow rates were maintained at 500mls/min and the blood pump speed varied between 80mls/min to 400mls/min depending on the patients' size.

3.3.2 Non-invasive blood volume monitor

Patients

I included all children who had undergone at least one month of HD within the dialysis unit at the Hospital for Sick Children, Toronto, excluding those receiving total parenteral nutrition or blood products (albumin, fresh frozen plasma, blood, platelets)

during their treatment and those who were acutely unwell. Patients were subdivided into 2 groups for the presence or absence of ‘polyuria’, which was defined as a daily urine output >1.5mls/kg/hr. Ethics approval for this study was granted by the local research ethics board and informed consent was obtained from patients or their guardians.

Baseline characteristics of the patients and dialytic treatments are listed in Table 3.1. The underlying renal disease was focal segmental glomerulosclerosis (FSGS)[1 patient], autosomal recessive polycystic kidney disease (ARPKD)[1 patient], renal dysplasia [4 patients], chronic allograft nephropathy and BK virus nephropathy secondary following a cardiac transplant[1 patient], membranous glomerulonephritis [1 patient], anti-neutrophil cytoplasmic antibodies (ANCA) negative glomerulonephritis [1 patient], unknown underlying aetiology [2 patients]. Of the 11 patients 5 were polyuric, one patient with panhypopituitarism was prone to hypotensive episodes, 1 patient had a chronic history of intradialytic cramping and 1 patient had been treated with a second heart transplant and had evidence of significant right ventricular dilatation on a peak dobutamine stress test but normal LV function at rest. 3 patients had LVH and 5 were hypertensive.

Table 3.1: Baseline characteristics of patients and their dialytic treatments

Sex (M/F)	6/5
Age (years)	12.8 [7 to 17]
Dry weight (kg)	40.2 [18.5 to 69.4]
Urine output (yes/no)	7/4
Urine output (mls/kg/hr)	1.61 [0.2 to 2.9]
Pre-dialysis plasma hemoglobin (g/l)	94.8 [114 to 84]
Pre-dialysis plasma albumin (g/l)	35.8 [26.5 to 44]
Pre-dialysis plasma ionized calcium (mmol/l)	1.24 [1.09 to 1.55]
Mean gross UF (mls/session)	1475 [500 to 3500]
UF range in non-polyuric patients	[1123 to 3500]
UF range in polyuric patients	[408 to 1600]
Blood flow rate (mls/min)	120-350
Dialysate flow rate (mls/min)	200-650
Kt/V	1.71[1.36 to 2.14]
Mean Systolic BP at the start of dialysis (mmHg)	113 [84 to 170]
Mean Diastolic BP at the start of dialysis (mmHg)	68.1 [49 to 95]
Mean Heart rate at the start of dialysis (beats/min)	100 [64 to 133]

Dialysis Prescription

All patients were dialysed using the Fresenius 2008K® or 2008H® for 3hrs, 4 times per week or for 4hrs, 3 times per week. In addition if patients arrived for their treatment grossly fluid overloaded and remained at least 1kg above their estimated dry weight (or 0.5kg in a hypotensive prone patient) at the end of dialysis, they returned the following day for an additional 2 hr treatment. All dialysis membranes were high flux, triacetate cellulose or polysulfone membranes. Dialysis flow rates varied between 200 to 650mls/min and blood flow rates were calculated to provide a urea clearance of 3 to 5mls/kg/min. All patients received unfractionated heparin as standard anticoagulation. A bolus dose of 15-20u/kg was administered at the start of dialysis followed by a

continuous infusion of 15-20u/kg/hr, stopping the heparin infusion over the last 30 minutes of dialysis. The rate of infusion was adjusted to maintain the activated clotting time (ACT) at 20-50% above baseline, with a maximum ACT of 220 seconds. If patients were considered to be at a high risk of bleeding no heparin was given. Patients were dialysed against 35mmol/l bicarbonate and 1.25mmol/l calcium dialysate solutions with a small quantity of acetate in the acidic component to stabilise the dialysate. The dialysis water quality was tested monthly and met national standards. The dialysate temperatures were set at constant value of 37.5°C. Patients were permitted to consume one meal during their treatments.

All patients were dialysed with either step or linear, decreasing sodium profiles, starting with a sodium concentration of 148mmol/l that dropped to a final concentration of 138 or 135mmol/l. This was combined with UF profiles (see Figure 3.3):

- constant UF rate profile [UF profile 0]
- decreasing step wise decline profile [UF profile 3]
- decreasing linear decline profile [UF profile 2]
- high UF rates interspersed between low rates [UF profile 6]

The maximum UF rate for any profile did not exceed 1.5 times the average rate. The dialysis prescription was adjusted monthly to achieve a urea reduction rate between 65 to 80% and an estimated Kt/V between 1.2 and 1.6¹¹⁵.

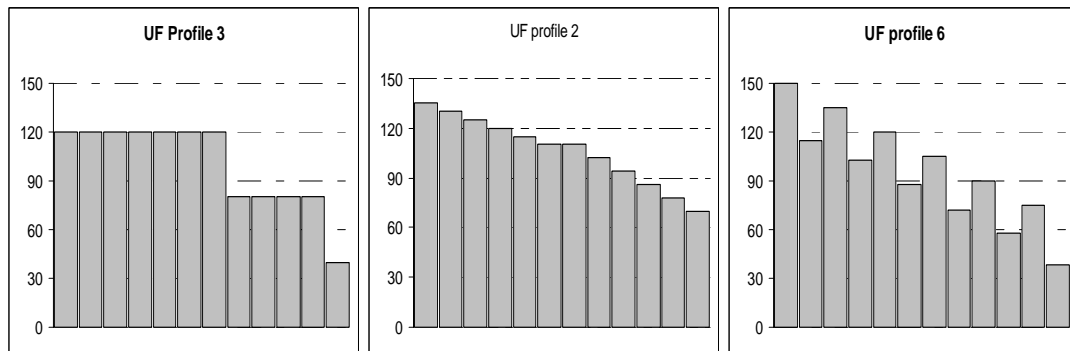


Figure 3.3: UF profiles

Study Protocol

During a mid-week or end of the week dialysis session RBV changes were measured using the Blood Volume Monitor® (BVM, Fresenius AG, Bad Homburg, Germany). Data was recorded hourly throughout treatment, at the time of an ‘adverse event’ prior to any nursing intervention and upon recovery. Concurrently, the patient’s heart rate and BP, and gross UF volume were recorded. A single BP reading was taken in a sitting position using an automated Dinamapp machine with a cuff adjusted for size. An ‘adverse event’ was defined as an intradialytic event that resulted in a nursing intervention (saline bolus, stopping UF, placing the patient in the Trendelenburg position, arrest call). Treatment failure was defined as the occurrence of an intradialytic adverse event and/or the development of hypotension defined as the first Task Force 5th percentile systolic BP measurements⁸. An exception was made for a hypotension prone patient with panhypopituitarism patient in whom the cut-off systolic BP was set at 75mmHg. Finally the dry weight was assessed monthly from a clinical assessment of the patient’s volume status combined with a review of post-dialysis weights at which the patient displayed no symptoms indicative of underhydration. If any degree of uncertainty remained the size of the cardiac silhouette and on a posterior-anterior view, post dialysis chest X-Ray.

Statistical analyses

All values of continuous variables were presented as mean \pm standard error. A paired t test was used to determine whether there were significant differences between continuous variables at the 95th confidence interval (CI), corrected for multiple comparisons using Bonferroni. In order to assess the ability of RBV changes to discriminate between successful and failed treatments receiver operating characteristics (ROC) curves were constructed:

- actual RBV measurement at the end of the first hour and treatment failure in the first or second hour of dialysis
- actual RBV measurement at the end of the second hour and treatment failure in the second or third hour of dialysis
- hourly RBV difference during the second hour and treatment failure in the second or third hour of dialysis. For example if the RBV was 90% at the start and 80% at the end of the second hour, the hourly RBV difference would be 10%.
- actual RBV measurement at the end of the third and treatment failure in the third or fourth hour of dialysis
- hourly difference in RBV during the third hour and treatment failure in the third or fourth hour of dialysis
- actual RBV measurement at the end of the fourth hour and treatment failure in the fourth hour of dialysis
- hourly difference in RBV during the fourth hour and treatment failure in the fourth hour of dialysis
- final RBV measurement at the end of dialysis and treatment failure

In the evaluation of actual RBV measurements, the ROCs were constructed taking low values to be 'positive' for treatment failure. For example, using a test threshold of 88%, the test is positive for a RBV of 88% or below and negative if the RBV is greater than 88%. In the analyses of hourly differences in RBV as the discriminator, high values were taken to be 'positive' for treatment failure. For example, with a test threshold of 10%, the test is positive if the hourly difference in RBV is greater or equal to 10% and negative if the hourly difference is less than 10%. Polyuric patients were excluded from the ROC analyses.

A repeated measures ANOVA was used to determine whether the rate of RBV change over time or the shape of the RBV curve differed between successful and failed treatments, testing for polyuria as a confounder. Measured RBV data from 60 minutes to the end of dialysis was entered into the analysis. Finally a logistic regression analysis, again with polyuria as a confounder, was conducted to test the relationship between treatment outcome (successful or failed treatment) and the predictors: i) final RBV measurement at the end of treatment; ii) difference in systolic BP from the start to the end of treatment; iii) difference in diastolic BP from the start to the end of treatment; and iv) difference between final and initial heart rate. For all four analyses 'end of treatment' was defined as the time of completing the prescribed dialysis treatment or the time at which an adverse intradialytic event occurred.

All statistical tests were performed using the SAS statistical package (SAS 9.1, North Carolina, USA). All statistical tests were two tailed with a p-value less than or equal to 0.05 taken to indicate significance. The internal correlation of observations from the same patients was taken into account by completing repeated measures analyses for all.

3.4 Results

From the 11 patients, 74 RBV curves were recorded of which 15 records were from polyuric patients. I have no information on the number of dialysis treatments and thus the number of RBV curves that were generated by each patient as I was blinded to the selection of patients for RBV analyses. Intradialytic hypotension occurred in 34% (26/74) of treatments, associated with RBV changes of up to 30%. Intradialytic symptoms occurred in 41% (30/74) of the treatments, 14% (10/74) were stopped prematurely and only 53% (39/74) of UF targets could match the volume of the intradialytic weight gain.

The hemodynamic response during HD differed between patients and is best demonstrated using specific examples.

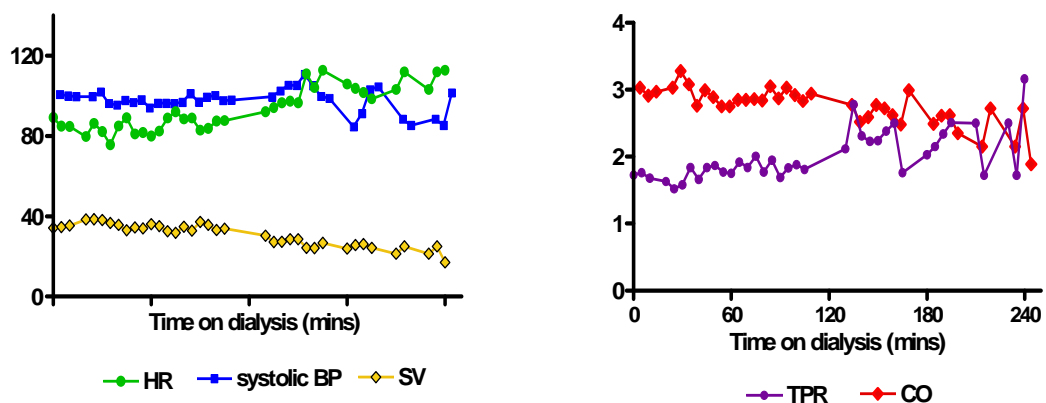


Figure 3.4: Intradialytic haemodynamic response for Patient 1

Patient 1 mounted a tachycardic response from the second hour of dialysis. She demonstrated a slow gradual decline in her SV and CO during the first 3 hours of dialysis with a sudden fall in both in the last hour of dialysis, associated with a drop in her BP. Her BP essentially mimicked the TPR and as her TPR became unstable in the

3rd and 4th hour her BP followed suit. Within the group this was a common feature. The systolic BP appeared to be most influenced by the TPR and thus if the rise in vascular resistance was inadequate, a declining BP followed.

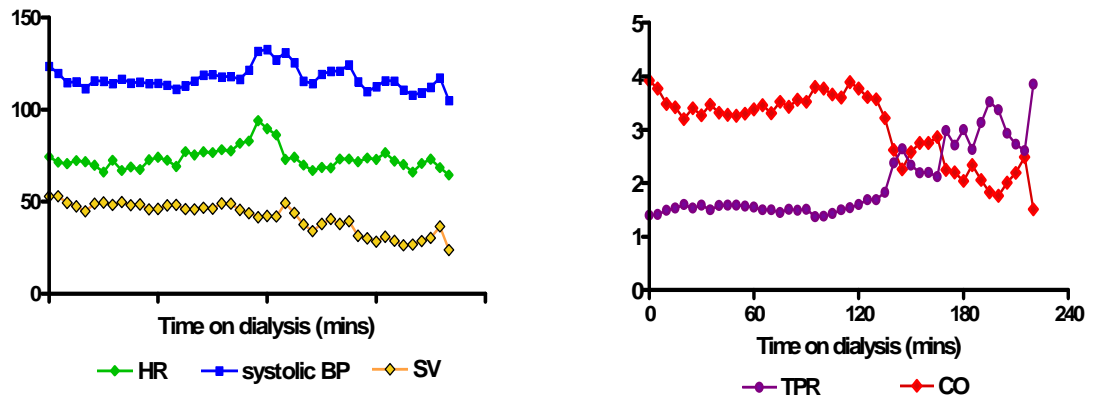


Figure 3.5: Intradialytic haemodynamic response for Patient 2

Patient 2 was haemodynamically stable for the first 2 hours of dialysis and then suddenly dropped his CO. This was preceded by a short-lived tachycardic response and followed by a fall in SV. The BP remained relatively stable up to this point and in fact increased at the same time as the patient became tachycardic. As the heart rate fell so did the SV and BP. The BP then stabilized as the TPR increased. Within the group the drop in CO was greatest featured in patients that failed to mount an adequate tachycardic response.

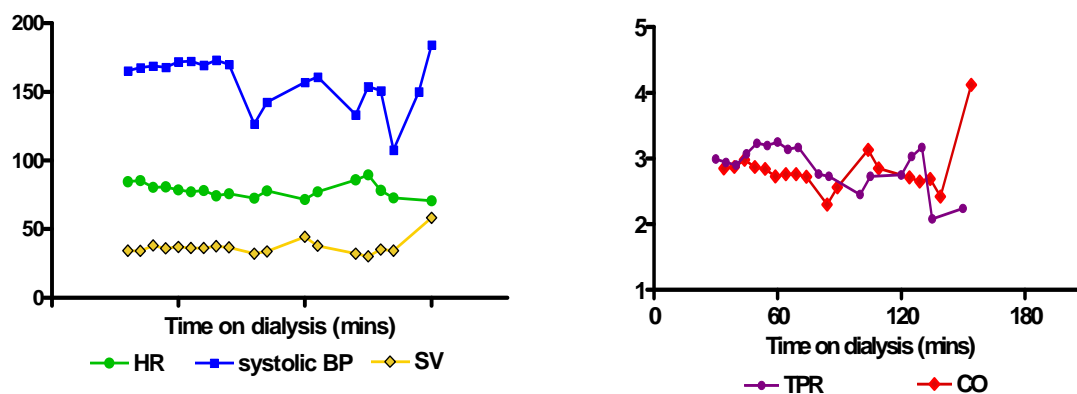


Figure 3.6: Intradialytic haemodynamic response for Patient 3

Patient 3 was a 13 year old with FSGS, oliguria, significant proteinuria and relative hypoalbuminaemia. She demonstrated a rising CO and SV during the 2nd hr of dialysis presumably due to refilling from the interstitial space. In spite of this, a delayed response in TPR resulted in a falling BP. The BP recovered as the TPR increased, in parallel with a rising CO. Please note in Patient 3 we were only able to capture data for the first 3 hours of dialysis as she did not tolerate the finometer.

The limited number of paediatric specific finger cuffs placed an age restriction of 11 years old, under which it was not possible to successfully collect data. Previous studies on neonates have reported success on using larger finger cuffs over the patients' wrists, however this method was also unsuccessful. The other major concern with the finometer was the fact that it was not tolerated by the children for long periods of time and it was only after a lot of cajoling and repeated efforts in some patients that I was able to complete the study.

The combined group trend, as illustrated below, showed a falling CO and SV and rising HR with time on dialysis. As the systolic BP fell in the latter half of dialysis the TPR increased. As a general rule hypotension was the result of a falling cardiac output (CO) combined with an insufficient rise in total peripheral resistance (TPR).

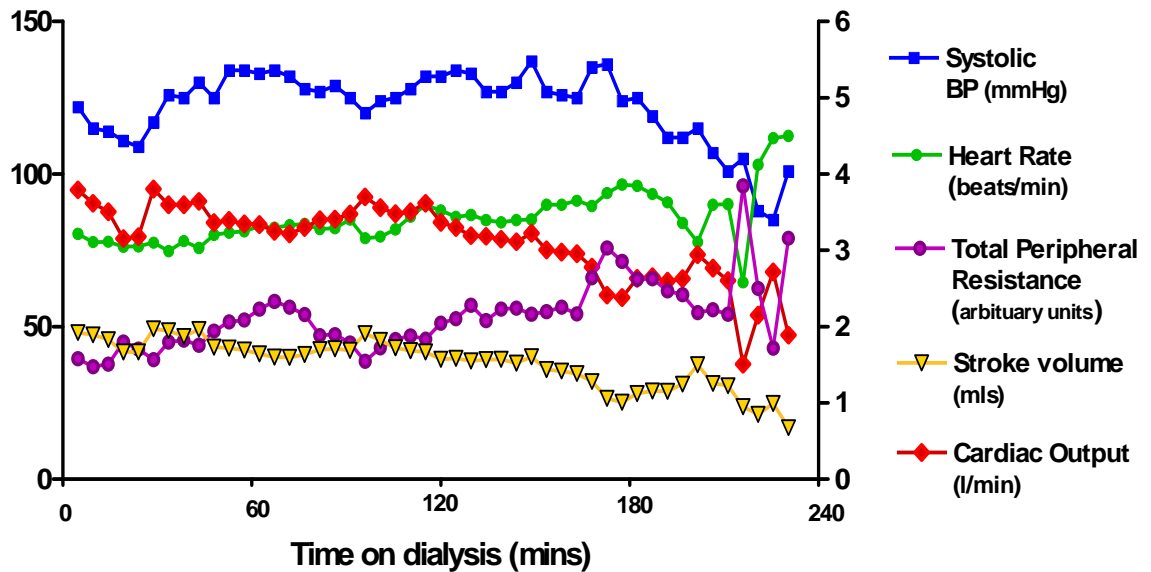


Figure 3.7: Graphical representation of the combined group trend

RBV as a Predictor of Outcome

Regression analysis demonstrated a significant association between change in systolic BP during a HD session and final RBV measurement ($p=0.05$), excluding data from polyuric patients (see Figure 3.8).

The presence of polyuria as a confounder had a highly significant effect on the final RBV reduction ($p<0.0001$), such that polyuric patients had higher final RBV measurements at the end of dialysis in both successful and failed treatments.

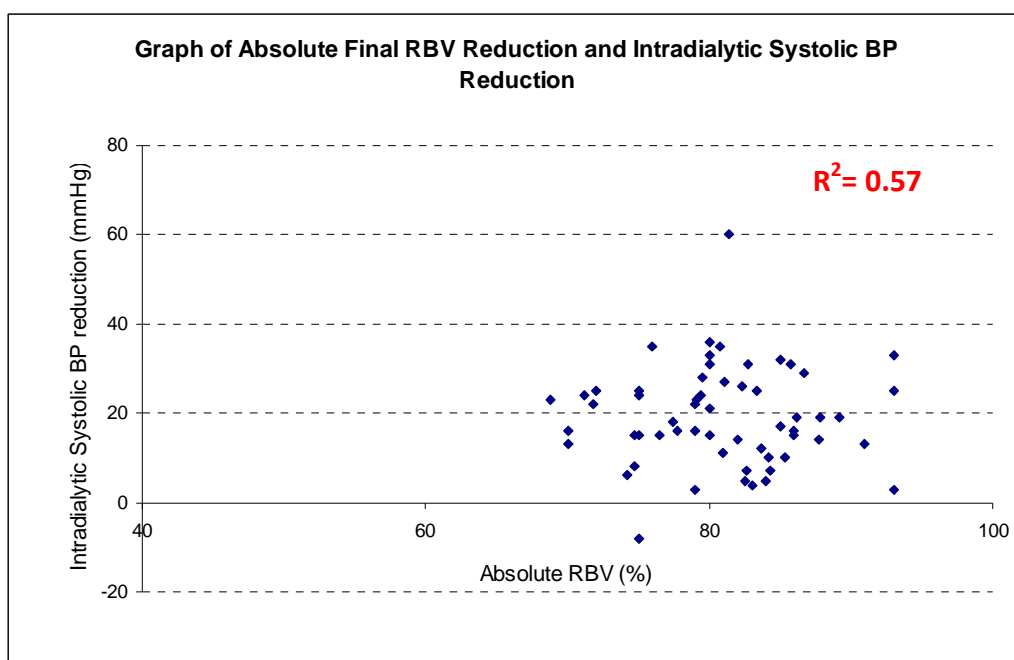


Figure 3.8: Graph of absolute final RBV reduction and intradialytic BP change

Multivariate logistic regression was used to test potential predictors of treatment failure (Table 3.2). The only variable significantly related to treatment failure was the difference in heart rate and the presence of polyuria as a confounder was not statistically significant. For each beat per minute increase in heart rate during dialysis there was a 5% increased risk of treatment failure ($p=0.05$).

Table 3.2: Logistic regression of complication free treatments in multivariate analysis

Group	p value	Odds ratio	95% Confidence Interval
Final RBV measurement at the end of dialysis (for each 1% increase)	0.27	0.95	0.88 – 1.04
Difference in systolic BP from the start to the end of dialysis (for each mmHg decrease)	0.11	0.97	0.926 – 1.01
Difference in diastolic BP from the start to the end of dialysis (for each mmHg decrease)	0.47	1.02	0.97 – 1.07
Difference between final and initial heart rate (for each beat/min increase)	0.05	0.95	0.92 – 0.99

The repeated measures ANOVA found no statistically significant difference in the rates of change of the RBV from 1 hour to the end of treatment between successful and failed treatments (Figure 3.9).

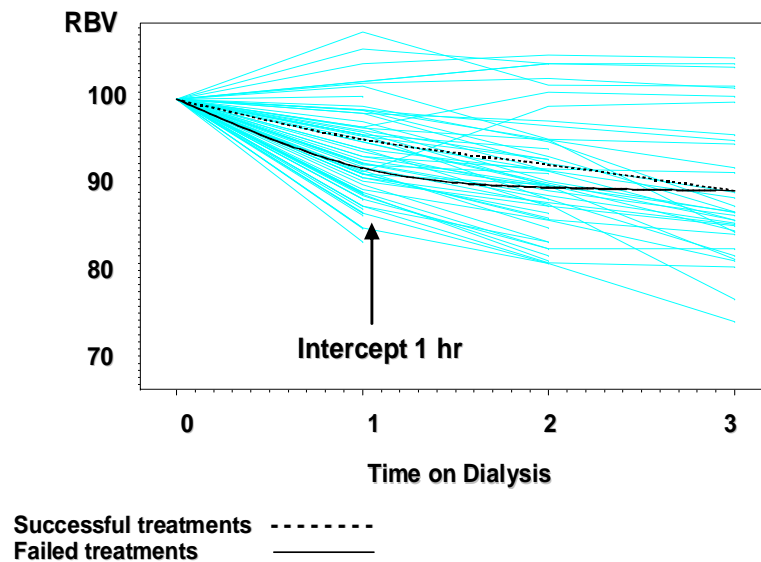


Figure 3.9: Individual RBV curves with group trends for treatments with and without complications

The cumulative data in the fourth hour was small and disproportionate, there was one treatment failure and 7 seven successful ones. To account for this bias we analyzed the data up to the end of the third hour and the fourth hour, but as the results were the same we have only reported on the analysis to the end of the third hour. The average RBV measurements were higher in the successful treatments but the shape of the RBV curve and the rate of RBV change from 1 hour to end of the third hour was not statistically significant if including all treatments ($p=0.50$) and or after excluding treatments from polyuric patients ($p=0.75$). There was a significant difference in the average RBV measurement at the point of entry into the ANOVA analysis, namely the time intercept 1 hour (see Figure 3.8). This translates to a statistically significant difference in the

average RBV measurement at 60 minutes of dialysis. Therefore the rate of RBV change during the first hour of dialysis between the successful and failed treatments was statistically significant with a steeper decline in the failed treatments (see Table 3.3).

Table 3.3: Differences in average absolute RBV measurements for treatments with and without complications at intradialytic time intercept 1 hour

Repeated Measures ANOVA for dialysis time intercept 1hr	Average RBV	p Value	95% Confidence Interval
<i>Including all RBV curves</i>			
Complication free treatments	90.1	0.01	87.95 – 93.35
Complicated treatments	86.1	0.01	83.96 - 88.21
<i>Excluding treatments from polyuric patients</i>			
Complication free treatments	86.1	0.05	84.07 – 88.22
Complicated treatments	83.6	0.05	82.05 – 85.07

One factor that was present in all the patients that may have influenced RBV change was the consumption of food. However it was not possible to test the relationship between the timing and the size of meal in the first hour and changes in RBD reduction as every patient consumed a meal and in 90% of cases patients tended to snack on foods such as crisps before or after their meal.

RBV Reduction as a Discriminator of Successful and Failed Treatment

We found actual RBV measurements at the end of each hour of dialysis to be better discriminators of outcome than hourly RBV differences. Using the hourly difference in RBV in the first, second, third and fourth hour, and final RBV measurement at the end

of treatment, the 95% CI for the ROC area under the curve (AUC) contained 0.5 (Table 3.4). Thus these tests are redundant as their application would only provide a 50:50 odds ratio of discriminating between outcomes and were thus excluded from any further analyses. ROC curves were only constructed for actual RBV measurements at the end of the first, second and third hours of dialysis. The ROC curves for the first hour can be seen in Figures 3.10 and 3.11

Table 3.4: Proposed RBV diagnostic tests and the empirical Area Under Curve (AUC) analysis of their ROC curves

Diagnostic Test	AUC	95% Confidence interval of AUC
Absolute RBV measurement at the end of the first hour	0.82	0.68 – 0.90
Absolute RBV measurement at the end of the second hour	0.79	0.62 – 0.89
Absolute RBV measurement at the end of the third hour	0.72	0.50 – 0.86
Absolute RBV measurement at the end of the fourth hour	0.50	0.20 – 0.71
Final absolute RBV measurement at the end of dialysis	0.50	0.34 – 0.63

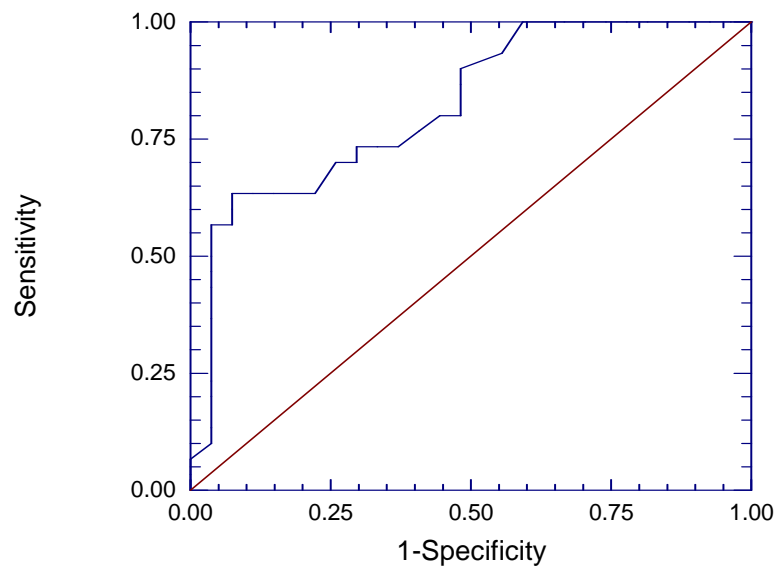


Figure 3.10: Empirical ROC for absolute RBV change at the end of the first hour of HD

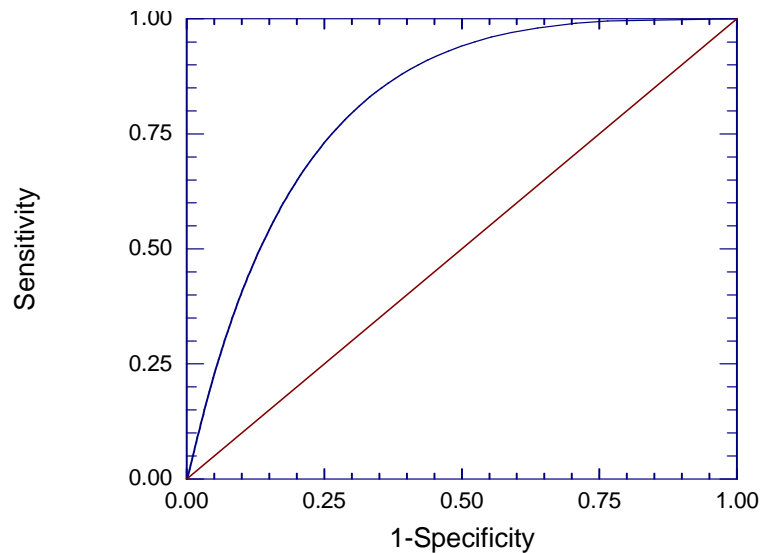


Figure 3.11: ROC curve of the absolute RBV change at the end of the first hour of HD based on the binormal assumption.

The best cut point on these ROC curves represented a RBV cut-off threshold of 88% at the end of the first hour, 84% at the end of the second hour and 82% at the end of the third hour. The predictive value of these thresholds for determining treatment failure is shown in Table 3.5.

Table 3.5: The predictive value of our ROC derived RBV thresholds testing for treatment complications

RBV Threshold	Sensitivity	Specificity	PPV	NPV
88% at the end of the 1 st hour of dialysis	63%	89%	86%	69%
84% at the end of the 2 nd hour of dialysis	58%	94%	96%	52%
82% at the end of the 3 rd hour of dialysis	78%	80%	91%	57%

Test 'Positive' if less than or equal to RBV threshold

Test 'Negative' if greater than RBV threshold

PPV- positive predictive value, NPV- negative predictive value

3.5 Discussion

The haemodynamic response during a 4 hour conventional HD treatment was different and individual to each child. Similarly there was an intra-patient and inter-patient variation in RBV profiles confounded by differences between patients with and without significant residual renal function. The gradient of the RBV curve in the first hour and changes in intradialytic heart rate were the strongest predictors for the occurrence of intradialytic adverse events.

The intradialytic blood volume is dependent on several distinct factors, the volume of the extracellular space, the dynamic balance between UF and vascular refilling during dialysis, vascular tone and the ability to mount an adequate cardiovascular response at times of decompensation. During the course of the dialysis session any one of these factors could predominate and therefore also be primarily responsible for precipitating hypotension. This would also explain the range of critical RBV thresholds that resulted in intradialytic morbidity or the variations in the nature of the compensatory response within patients. The analyses of the polyuric patients highlighted the relevance of an additional factor, the hydration status of a child. One can hypothesise that patients with a high urine output have minimal intradialytic volume expansion and their presenting weight is almost identical to their euvolaemic target weight. Therefore minor changes in the blood volume could result in hypovolaemia at higher RBV thresholds. At the other extreme, in fluid overloaded patients a poor correlation exists between changes in body weight and plasma volume with an inverse relationship between pre-dialysis BP and intradialytic changes in the plasma volume¹¹⁶. Theoretically therefore, chronically fluid overloaded patients or those with an over-estimation of their dry weight should be able to achieve higher UF volumes without compromising their circulation.

The cardiovascular system demonstrates a high degree of intrinsic autoregulation dependent on neural, hormonal and local metabolic control all of which are sensitive and affected by disease. Uraemia alters the physiological mechanisms involved in maintaining arteriolar tone and cardiac output. Tachycardia is an early and universal response to all causes of intravascular compromise¹⁰⁵ and this remains true during paediatric HD. The tachycardic response was important both in predicting intradialytic morbidity and supporting the cardiac output. This would suggest that in the presence of uraemia the chronotropic response dominated over the ionotropic response. In fact recent adult data concurs with this notion. HD induces segmental myocardial dysfunction and even in the presence of the significant haemodynamic stress imposed by UF the ejection fraction does not rise¹¹⁷. These findings raise the possibility that HD negatively affects myocardial contractility not only in adults but perhaps in children too.

Analogous to newborns, patients with ESRD have increased basal level peripheral sympathetic nervous system activity¹¹⁸. In newborns this is associated with a relative resistance to the effects of catecholamines and thus increases in heart rate achieve little gain in cardiac output, and if excessive may even drop the cardiac output. If we apply the same physiology to uraemic children one can explain how the tachycardic response is useful in predicting adverse events during dialysis but on its own is unable to prevent hypotension from occurring. In reality this is all postulation as I have no evidence to support whether this is the pathogenesis for the limited compensatory response in children on dialysis, nevertheless I present data that is clearly indicative of a change in cardiovascular phenotype in uraemic patients.

Children with ESRD show evidence of endothelial dysfunction, reduced vessel compliance²⁴ and vascular calcification¹¹⁹. Above this baseline risk the very act of dialysis is thought to initiate further endothelial dysfunction. Adult HD patients have elevated levels of endothelial cells and endothelial microparticles¹²⁰, reduced endothelial progenitor cell function¹²¹ with preservation of smooth muscle progenitor cells¹²². This translates to a vascular environment conducive to injury but without the capacity to repair, with triggers that are almost certainly multi-directional. Dialysis is recognised as a pro-inflammatory procedure but the mechanisms continue to elude us. UF with RBV reductions as high as 30% as demonstrated in this study alter blood viscosity and shear stress and this can adversely influence endothelial cell survival and quiescence. Severe reductions in afterload during dialysis can induce ischaemic endothelial cell apoptosis with continued and repeated depletion of the body's pool of endothelial progenitor cells. The resultant endothelial dysfunction represents a molecular state of activation and a switch from a quiescent phenotype towards to one that is procoagulant, pro-inflammatory and vasoconstrictive. This is clearly counter-productive and in all likelihood responsible for the maladaptive regulation of vascular tone and the increased predisposition to hypotension. During paediatric HD this may be especially important as peripheral vascular resistance was in this cohort one of the strongest influences on systolic BP.

Similar to findings in adults, the absolute RBV reduction was unable to predict intradialytic hypotension. Dasselar et al found a significant difference in RBV change measurements by different NIVMs (the Crit-Line, Hemoscan, and BVM) and those obtained from laboratory-derived haemoglobin changes¹²³. This raises a suspicion of an inherent flaw within all NIVMs that produces inaccuracies. RBV is based on the

principle of mass conservation and an assumption that the total amount of blood constituent in the circulation is constant, with uniform mixing of red blood cells and plasma throughout the circulation or that the relative distribution of blood constituents over different vascular beds does not change during dialysis. We now know this assumption to be incorrect. Whole blood haematocrit is lower than arterial or venous haematocrit due to the dynamic reduction in microvascular haematocrit in capillaries and venules (Fahraeus effect)¹⁵. The difference is expressed as a F-cell ratio and approximates 0.91 in the normal population¹²⁴. During HD, owing to the redistribution of the blood from the microcirculation to the central circulation the F-cell ratio increases and thus the observed RBV change in theory underestimates the whole body blood volume change¹²⁵. In fact Agarwal et al tested the diagnostic ability of the RBV slope in detecting volume excess and volume depletion. They found that the area under the ROC curve was 0.71 to predict volume excess and 0.55 to predict volume depletion¹²⁶ and hence RBV curves were superior in discriminating between volume excess than volume depletion. Therefore the RBV curve lacks potential in predicting the critical point in intravascular volume reduction and the onset of decompensation and this may in part be explained by the delay in detecting real changes.

This study may not have been able to identify a universal absolute RBV threshold that predicts intradialytic morbidity but I was able to determine and validate RBV thresholds that discriminated between treatments with and without adverse events. Jain et al have proposed similar RBV driven UF algorithms and in contrast to my cut-off RBV thresholds of 88% at the end of the first hour, 84% at the end of the second hour and 82% at the end of the third hour, they defined safe UF with a RBV reduction less than 8% per hour in the first 90 minutes and less than 4 % thereafter⁴³. The reality is that

both may in fact be valid and the discrepancy relates to differences in the dialysis prescription and choice of NIVM. The Blood Volume Monitor® measures the difference in blood density and is dependent on the total protein concentration and the Crit-line®, the device used by Jain measures the red blood cell concentration through assessment of the optical density of whole blood. There is no doubt that the accuracy of readings between the two devices is similar however the RBV measurements are not directly interchangeable. Schneditz et al demonstrated a 2% difference in relative blood volume changes (BVM 2% less reduction in blood volume compared to Crit-line) that developed approximately 1 hr into dialysis, and persisted thereafter⁴¹. The dialysis prescription is also relevant to this discussion. Jain studied patients dialysed against a fixed dialysate sodium concentration of 140mEq/l and provided no details on UF rates. In contrast the objective of this study was to validate RBV thresholds over a range of dialysis sodium and UF prescriptions thus making it more broadly applicable clinically. The theoretical problem with this approach is that we know that dialysate sodium and UF rates influence dialysis quality and risk of intradialytic symptoms and hypotension^{78, 127}. In an attempt to address this possible bias I tested the possibility of an independent effect of the dialysis prescription on the frequency of adverse events. By entering my data into a repeated measures Generalized Estimating Equations model I analysed the odds of adverse events between the UF profiles and two sodium profiles and found no statistically significant differences between the groups. Thus I present RBV thresholds that have the potential to guide safe UF but would recommend against prescriptive application of these thresholds as adjustments may be required with local differences in dialysis conditions.

3.6 Study limitations

First and foremost my study was performed in a small and heterogenous population. However as this was the formal first assessment of this kind in children my initial aim was not to be over restrictive on the recruitment process. In the world of paediatric HD where single centre patient numbers rarely exceed 20, maintaining such a broad inclusion criteria was necessary in order to achieve an adequate and appropriate cohort size. Clearly in the converse it also has the potential to introduce bias.

Treatments were not standardized for patient factors such as postural changes during dialysis and food intake which are known to influence the accuracy of NIVM and cardiovascular dynamics. Similarly sodium and UF profiles, and the use of short intervals of isolated UF are all dialysis factors with the potential to influence cardiovascular stability during dialysis. The results should therefore be interpreted within the limitations of its design.

The numbers were further depleted in the finometer study owing to the restrictions imposed by the size limitations of the finger cuffs. The smallest finger cuff size was only suitable for children 11 years or over and hence we were unable to get any data on 6 patients. Previous studies on neonates have reported success on using larger finger cuffs over the patient's wrist, but in my hands this method failed to produce an adequate trace and was therefore abandoned. The other major concern with the finometer was the fact that it was not tolerated by the children for long periods of time. The cuff had to be wrapped tightly around the finger for the finger-clamp method to be effective and the longer the cuff remained in place the greater the likelihood of adverse symptoms. Children complained of the finger becoming numb, white and cold to touch. The wrist

strap that housed all the sensors and adaptors was also relatively heavy and cumbersome and this prompted several verbal complaints. The design of the finometer was such that it was reported to be able to cope with movements in the arm without having a negative impact on the trace. However this did not match my own experience. Typically a child on dialysis would eat lunch, watch TV, play games or was encouraged to do their homework. In the children studies the resultant movement from these activities frequently resulted in sensor failure and repeated interruptions in the trace.

Clearly a child's cooperation is paramount to attaining finometer data and on reflection I feel that the method used in this study will require change during subsequent studies. The objective in dialysis studies is to measure changes in haemodynamic variables with time on dialysis. In theory this can also be achieved by attempting finometer traces for 15-30minute intervals per hour of dialysis. If the first time aliquot starts prior to the patient being connected, baseline information will be captured while the final 30 minutes will capture the period at the end of dialysis and hence the time of peak stress in addition to the recovery period during washback and disconnection from the dialysis circuit. I am also hoping that by allowing the children respite time, free from the finometer, compliance and co-operation may improve.

The other major limitation of this study was the fact that the two arms of the study were conducted in different patients. The Hospital for Sick Children, Toronto had already invested in NIVMs and hence this study was possible there. In contrast Great Ormond Street Hospital had access to the finometer but not NIVMs. This preliminary data has been very useful in determining group trends and directing future studies but there is no doubt that to accurately assess trends in individual patients simultaneous data from both

the finometer and RBV monitoring is required. This would also be more in keeping with the future direction of HD treatments, that of individualised treatments.

3.7 Conclusion

In conclusion the hemodynamic response to conventional HD treatments and UF is different and individual to each child. The evolution of tachycardia and the gradient of decline of the RBV curve during the first hour of treatment can be useful in predicting the occurrence of intradialytic adverse events. The blood volume profiles from patients with significant residual urine output were different from oligo-anuric patients.

Cut-off RBV thresholds of 88% at the end of the first hour, 84% at the end of the second hour and 82% at the end of the third hour were the best discriminators of outcome with a high specificity and PPV for treatment failure but limited sensitivity and NPV. Knowledge of patient specific adaptive responses may allow us to target interventions in supporting circulation during subsequent dialysis sessions.

Chapter Four

Myocardial Consequences of Haemodialysis

4.1 Hypotheses

- Uraemic children have a predisposition for demand ischaemia
- The extracorporeal blood volume necessary for priming the HD circuit combined with the intravascular fluid depletion during UF amounts to a significant haemodynamic stress.
- The resultant effect is HD induced cardiac perfusion defects and regional myocardial dysfunction
- Speckle tracking two-dimensional strain is more sensitive in detecting ischaemic myocardial dysfunction than assessment of regional wall motion activity.

4.2 Introduction

Cardiovascular mortality is grossly elevated in HD patients. CKD have a 30 fold increase in mortality than age-matched controls and an even higher risk of up to 800 fold for dialysis and young adults²⁰. This excess of cardiovascular death is only partly explained by an increase in traditional risk factors, and several mechanisms of cardiac damage specific to the uraemic milieu have been identified. It is also becoming increasingly apparent that HD in itself confers a risk but the pathophysiological mechanisms remain elusive. In adults there is evidence from isotopic⁶⁵, electrocardiographic^{60, 128}, biochemical^{58, 59} and echocardiographic^{100, 117} studies implicating HD as a source of recurrent subclinical myocardial cell injury, even in the absence of pre-existing large vessel epicardial coronary artery disease (CAD). Single photon emission computed tomography (PET) adult data has demonstrated acute reductions in global and segmental myocardial blood flow during HD, with matched reversible reductions in segmental contractile function⁶⁵, consistent with the definition

of myocardial stunning⁵⁵. The number of stunned segments and the intensity of stunning within segments correlate with intradialytic BP changes and UF volume¹²⁹. In the model of CAD, repeated stunning leads to myocardial hibernation with resultant heart failure⁷¹. Within dialysis patients transient myocardial ischemia precipitates cardiac arrhythmias¹³⁰ and progresses to fixed regional systolic dysfunction and reduced global systolic function⁶⁷.

Uraemic children and young adults have a similar constellation of ischaemia predisposing factors to adults, including increased intima media thickness and pulse wave velocity, vascular calcification, early atherosclerosis and endothelial dysfunction^{24, 119}, but without significant atheromatous CAD. In the previous study I have demonstrated that the incidence of HD induced haemodynamic disturbance is comparable to adults, with a 20-30% incidence of intradialytic hypotension associated with a relative blood volume reduction of 20-25%. It is therefore plausible that children may also display a similar pathophysiology of dialysis induced cardiac injury as a result of characteristic uraemic cardiovascular abnormalities.

Regional wall motion assessment (RWMA) is primarily an assessment in the longitudinal axis and uses the inward motion of endocardial borders as the sole marker of abnormal contraction. In contrast 2D speckle tracking provides a multi-axis assessment of LV function employing functional components that are not visible to the naked eye. Speckle tracking strain is also both translation and angle independent with lower inter and intra-operator variability compared with RWMA¹³¹ in adults. This makes it a very promising novel technique for detecting regional LV dysfunction,

especially within this context. Uraemic children have no evidence of epicardial coronary artery disease and thus the extent of ischaemic injury may be mild and findings subtle.

4.3 Method

4.3.1 Patients

All patients at Great Ormond Street Hospital that had been on HD for at least one month were considered for inclusion within the study. I excluded those patients with congenital heart disease, a concurrent respiratory illness or if it was not possible to obtain echocardiographic images of sufficient quality to allow meaningful analysis owing to poor windows for visualizing the heart. Ethics approval for this study was granted by the local research ethics board and informed consent was obtained from patients or their guardians.

Table 4.1: Patient Demographics

Patient	Age (yrs)	Time on HD (mths)	Cause of ESRD	AV fistula	LV septum [Z-score]	LV Posterior wall [Z-score]
*§ 1	5	4	Renal dysplasia	yes	1.3	1.7
*§ 2	17	89	Cystinosis	yes	1.6	0.3
*§ 3	15	43	Focal segmental glomerulosclerosis	yes	0.1	1.4
*§ 4	15	4	Renal dysplasia	yes	0.3	0.2
*§ 5	15	32	Focal segmental glomerulosclerosis	yes	2.6	1.9
*§ 6	13	4	Renal dysplasia	no	5.9	6.3
*§ 7	11	35	Renal dysplasia	yes	0.5	-0.6
*§ 8	13	15	Focal segmental glomerulosclerosis	no	0.6	-1.1
*§ 9	2	7	Glomerulocystic disease	no	1.5	1.7
* 10	17	12	Reflux nephropathy	yes	1.9	1.7
* 11	7	62	Autosomal recessive polycystic kidney disease	yes	1.0	0.3
*§ 12	14	6	Cystic dysplasia	yes	2.6	1.2
§ 13	13	2	Focal segmental glomerulosclerosis	no	0.4	0.3
§ 14	2	2	Nephronophthisis	no	1.2	1.3
§ 15	1	2	Oxalosis	no	0.7	0.8
§ 16	8	24	Congenital nephrotic syndrome	no	n/a	n/a
§ 17	15	2	Renal dysplasia	no	1.4	1.6

n/a: not available

AV fistula: arteriovenous fistula

LV: left ventricle

* Patients recruited for the *Regional wall motion Study*

§ Patients recruited for the *2D strain Study*

Of the 17 patients 9 had AV fistulae as their dialysis vascular access and in the remainder central tunnelled venous catheters were used. 5 patients had previous failed transplants and 2 patients had three months of peritoneal dialysis prior to HD. Residual urine output varied amongst the study group, 7 patients were anuric, 5 patients passed less than 1ml/kg/hr of urine and 5 patients passed between 1-2 mls/kg/hr. At their baseline examinations only one patient had LV hypertrophy and three patients had borderline hypertrophy (see Table 4.1

4.3.2 Dialysis Prescription

All patients were dialysed using Gambro 200S® dialysis monitors. Patients received HD for 4 hours, 3 times per week. All dialysis membranes were high flux polysulfone or triacetate cellulose membranes using sizes that at minimum were equivalent to each patient's body surface area. For all treatments the dialysate contained sodium 140 mmol/l, potassium 2mmol/l, calcium 1.75mmol/l, magnesium 0.5mmol/l, bicarbonate 34mmol/l with a small quantity of acetate in the acidic component to stabilise the dialysate. The dialysate temperature was set at a constant value of 37.0°C. Dialysate flow rates were maintained at 500mls/min and blood pump speeds varied between 80mls/min to 400mls/min depending on the patients' size. The dialysis prescription was adjusted monthly to achieve a urea reduction ratio greater than 65% and Kt/V urea greater than 1.2 (calculated from Daugiradas single pool kinetics)¹¹⁵. All patients received unfractionated heparin as required. Patients were permitted to consume one meal during their treatment. For each session, net fluid removal was set on an individual basis and adjusted to restore the patient to their ideal dry weight (clinically determined) by the end of the dialysis session. UF took place in parallel with dialysis using constant

UF rates unless patients had higher than normal UF requirements. In these circumstances patients received 30 minutes of isolated UF at the beginning and/or the end of the HD session.

4.3.3 Regional wall motion assessment

Technique

Using 2-dimensional (2D) echocardiography standard apical 2-chamber and 4-chamber views are taken to visualise the LV endocardial border in 2 planes at 90 degrees to each other. These images are then copied onto CDs in DICOM format for off-line analysis using a personal computer based digitising programme (Echo-CMS, MEDIS, Leiden, The Netherlands)¹³². Three consecutive heartbeats were analysed for each time point (extrasystolic beats were excluded). Endocardial borders (excluding papillary muscles) were traced semi-automatically for each videoframe of the 3-beat sequence, and any anomalies corrected manually. Maximal displacement of the endocardial border from a centre point was then measured over each of 100 chords around the LV wall, corrected for end-diastolic LV circumference (see Figure 4.1) and expressed as percentage shortening fraction (SF). Each apical view was divided into 5 segments and SF for the chords in each segment was averaged so 10 regions of the LV were assessed at each time point. Any segmental endocardial border that was not clearly visible was excluded from analysis. Segmental reduced regional wall motion (RRWM) was defined as a decline in SF of >20% from baseline and degrees of hyperkinesis 20% and 50% were defined as those segments that demonstrated a increase in SF of >20% and >50% respectively. I calculated the mean SF for all ten segments ($SF_{[Overall]}$), for those segments that developed new RRWM ($SF_{[RRWA]}$) and those segments that did not

develop RRWM ($SF_{[Non-RRWM]}$). Ejection fraction (EF) was calculated from the apical four chamber and 2 chamber view by the Simpson's rule. The LV posterior and septal wall thickness was measured from parasternal long axis M-mode images, and represented as Z-scores after adjusting for age and body surface area.

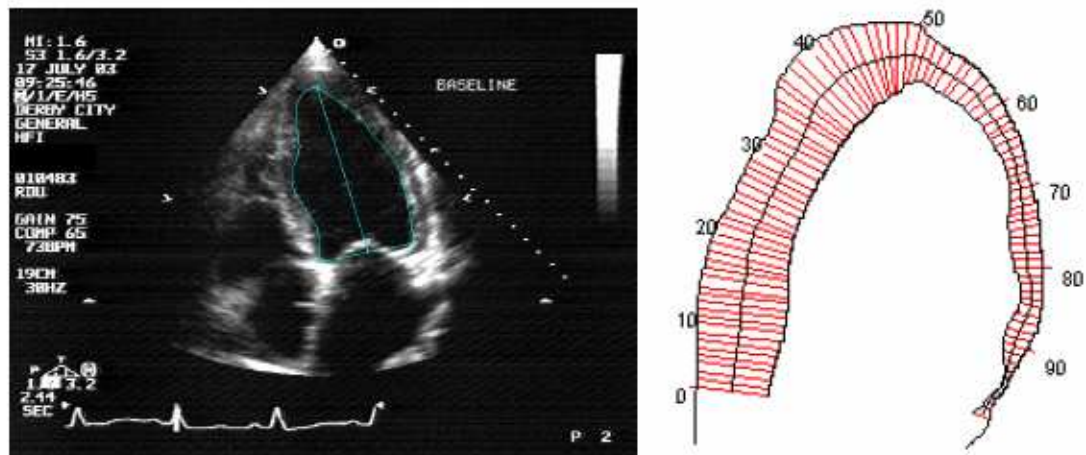


Figure 4.1: Assessment of regional wall motion activity by Echo CMS.

On the left panel highlighted in blue is an example of a semi-automatic tracing of the endocardial border. On the right panel each red line represents a measurement of the regional endocardial border movement.

Study Protocol

For each monitored dialysis treatment, serial echocardiography was performed at the start of dialysis (baseline), 2 hours into the dialysis session, the end of the dialysis session and at recovery 15mins after dialysis, once a saline wash-back had been given and the patients had been disconnected from the machine. Ideally I would have preferred a longer period post dialysis prior to re-assess the cardiac function, but owing to travel times and other social reasons patients refused. Blood samples were collected before and after each session in lithium heparin and EDTA tubes, and biochemical

analysis performed on a multichannel autoanalyser for routine electrochemical, full blood count and high sensitivity C-reactive protein (hsCRP). Cardiac troponin-I (cTnI) analysis was performed using a chemiluminescent assay on a Beckman Access Immunoassay analyser. Pre dialysis blood tests were drawn immediately after insertion of access needles or catheter connection, and post levels were taken from the arterial line after reducing the blood pump speed to 50ml/min. During each dialysis session the net UF volume and intradialytic symptoms with corresponding heart rate and BP measurements were recorded. For each patient echocardiography data was collected during two separate dialysis sessions, separated by no more than four weeks. The primary endpoint of HD induced myocardial stunning was determined from the degree of change in LV segmental SF, and the number of segments involved. The secondary endpoint was to assess whether a relationship existed between reduced segmental LV function and intradialytic BP and UF volume.

Statistical analyses

The data comprised of 2 data sets of 12 from the same patients. Therefore in order to determine the prevalence of myocardial stunning only one data set was used, selected at random, by tossing a coin. To test the association between dialysis and patient related factors and the severity of stunning I was able to combine the data sets by incorporating a repeated measures analysis into the analysis.

The results were expressed as mean \pm SD if parametric or the median and interquartile range (IQR) if non-parametric. Echocardiographic and haemodynamic data were analysed using one-way analysis of variance (ANOVA), with a design for repeated measures. Depending on Gaussian distribution, all other data were analysed using either

the paired or unpaired t tests or the Mann-Whitney or Wilcoxon matched pair tests. To test for the association between both the mean %SF_[RRWM] and SF_[non-RRWM] at 240 minutes against dialysis related factors (UF volume-mls/kg dry weight, intradialytic BP) and patients related factors (dialysis vintage, age) I used univariate regression analysis adjusting for repeated measures. I did not attempt multivariate logistic regression analysis due to the relatively small sample size. In all analyses, an alpha error at $p < 0.05$ was judged to be significant.

4.3.4 Speckle tracking two-dimensional strain assessment

Technique

The speckle tracking strain software analyzes motion by tracking ‘speckles’ from frame to frame in 2D echocardiogram images. Speckles are natural acoustic markers of 20-40 pixels that are equally distributed throughout the myocardium. By following the movement of each speckle throughout a single cardiac cycle a temporal assessment of myocardial muscle deformation is achieved (see Figure 4.2).

Standard grayscale 2D images were acquired in the 4-chamber apical views and parasternal short-axis views at the level of the papillary muscles (the level of mid wall contraction) using frame rates of 50 frames per second minimum. The apical images were required to assess peak longitudinal strain and the parasternal images for radial and circumferential strain. The images were stored digitally in raw format for analysis later. From an end-systolic single frame a region of interest was traced on the endocardial border by a point-and-click approach. The 2D strain algorithm then automatically evaluates the tracking quality at each myocardial region over time and

assigns each segment an ‘acceptable’ or non-acceptable’ label. For each image that was analysed the region of interest was manually adjusted until all the segments had acceptable tracking quality. The specialist software then processed and generated LV segmental time-strain curves from which the timing and value of peak strain per segment were extracted. For the purpose of 2D speckle tracking the LV was divided into 6 segments as shown in Figure 4.3.

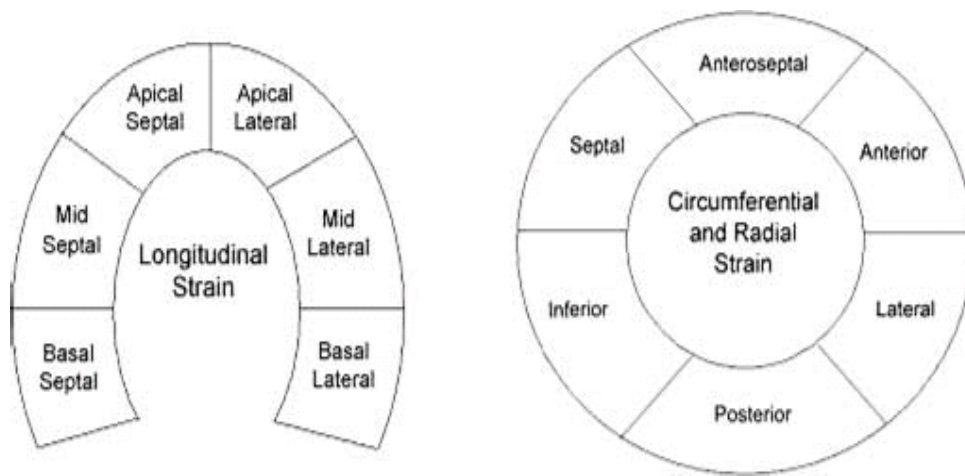


Figure 4.2: LV segmentation in the long axis (left) and short axis (right) for the purpose of regional strain measurements.

Speckle tracking for assessment of cardiac motion and dyssynchrony has been validated in adults with intraobserver and interobserver variability of 3.6% to 5.3%¹³¹ but the experience in children is extremely limited¹³³.

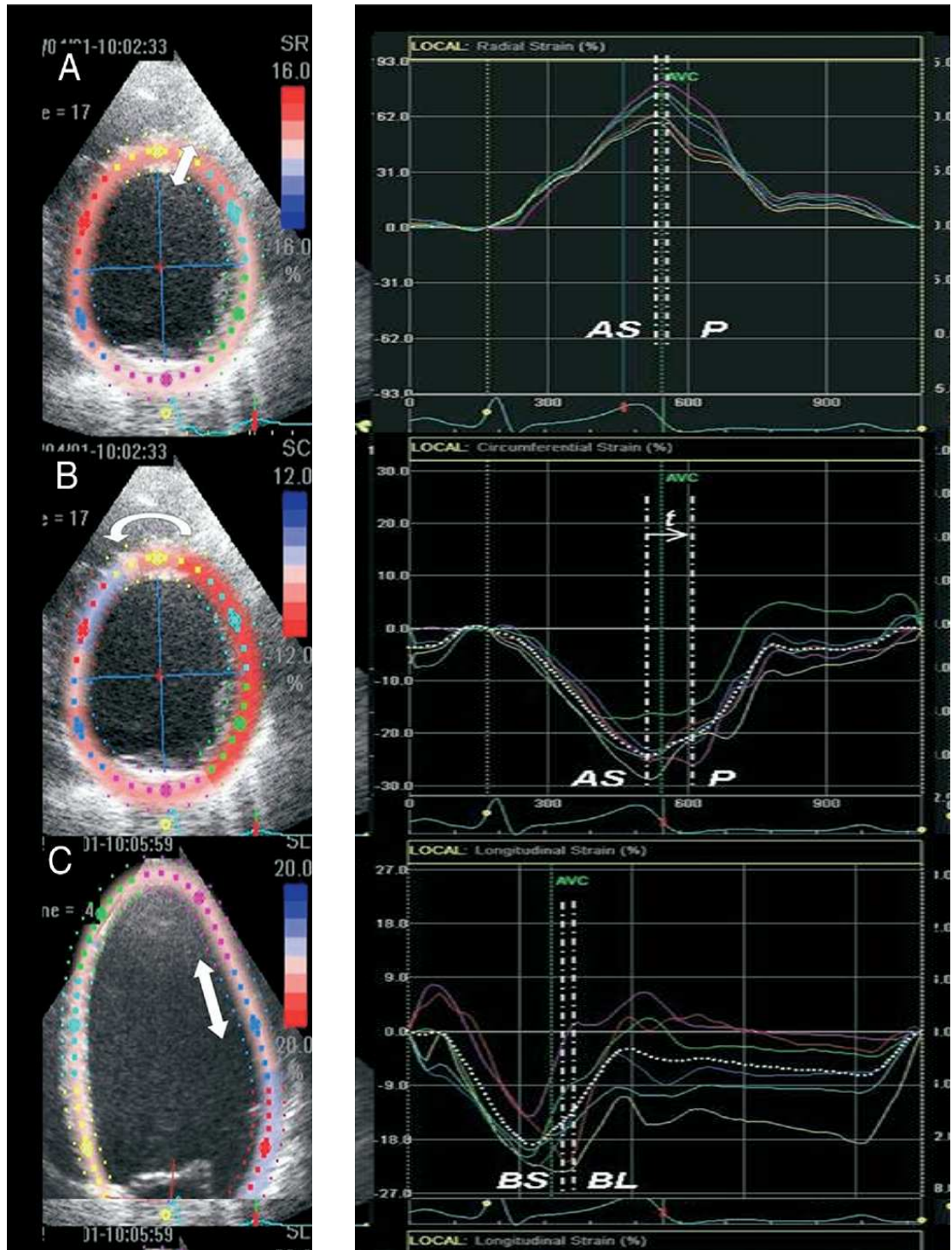


Figure 4.3: Two-Dimensional Strain Imaging.

In the left panels the strain images are represented. The arrows highlights the type of deformation assessed in each view: radial thickening (A), circumferential shortening (B), and longitudinal shortening (C). The right panel demonstrate the segmental time-strain curves for a synchronous left ventricle AVC refers to aortic valve closure and represents the end of systole. [Adapted from Delgado¹³⁴].

Study Protocol

For each monitored dialysis treatment, echocardiography was performed at the start of dialysis (baseline) and again at the end of the dialysis session, the time of peak stress. During each dialysis session intradialytic symptoms with corresponding heart rate and BP measurements were recorded in addition to the net UF volume at the end of each treatment. The images were then analysed with specialist 2D speckle tracking software to generate segmental longitudinal, radial and circumferential time strain curves. For each time point the peak segmental strain was recorded. To test for dyssynchrony two parameters were used, i) the maximal time delay between peak strain of 2 segments and ii) asynchrony index, which was derived by calculating the standard deviation of time to peak strain over the 6 segments.

Finally speckle tracking 2D strain assessments were performed on age matched controls at rest using longitudinal and parasternal (papillary muscle level) 2D echocardiographic grayscale images.

Statistical analyses

Echocardiographic and haemodynamic data differences within patients at the start and end of HD were analysed using ANOVA, with a design for repeated measures. Pearsons correlation analyses were performed to assess the relation between intradialytic strain reduction and dialysis related factors (UF volume-mls/kg dry weight, intradialytic BP) and patients related factors (dialysis vintage, age). Univariate linear regression analyses were used to determine predictors of intradialytic BP change. In all analyses, an alpha error at $p < 0.05$ was judged to be significant.

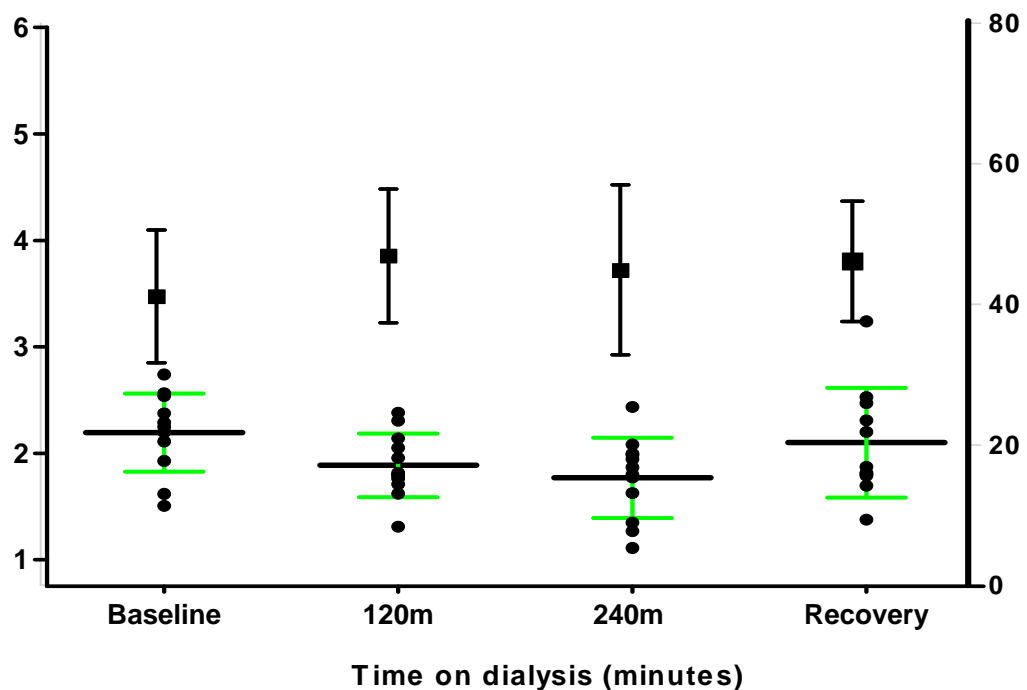
4.4 Results

4.4.1 Regional wall motion assessment

Global & Segmental Ventricular Function

The median LVEF was 51.8%, range 38.2 to 68.1 at baseline, 55.7% (44.2 to 66.7) at 120mins of HD, 53.21% (37.8 to 71.5) at 240mins and 55% (43.5 to 64) on recovery 15 minutes after dialysis (see Figure 4.4), but the differences between all the time points were not statistically significant ($p=0.56$). At the start of dialysis 4 patients had LVEF below the lower limit of normal, namely 50%.

Figure 4.4: Changes in global and segmental LV function during HD

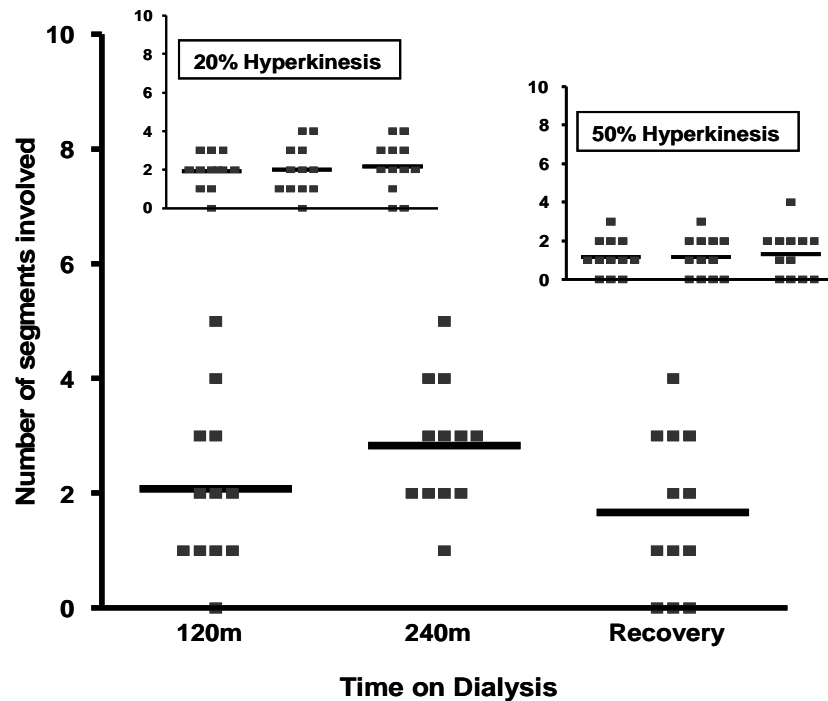


* Ejection fraction is represented as mean and standard deviation. The difference at the 4 time points was not statistically significant ($p=0.56$)

† Mean segmental %SF_[Overall] represented as the cohort mean and box plot of the individual results. The difference between the baseline and both 120m and 240m was statistically significant ($p<0.05$)

All 12 patients developed segments with RRWM in 1-5 segments (see Figure 4.5), with co-existing 20% hyperkinesis in 1-4 non stunned segments in 11/12 patients from 120mins that persisted into recovery. In addition 9/12 patients exhibited 50% hyperkinesis in as many as 3 segments. Again this was evident at 120mins and persisted into recovery (see Figure 4.5), Of the 35/120 segments that stunned mid-cavity segments dominated followed by basal and then apical segments.

Figure 4.5: Segmental RRWM and hyperkinesis during HD



The resultant effect on segmental shortening fraction was a fall of the mean segmental %SF_[Overall] from 2.2 ± 0.4 (mean \pm standard deviation) at baseline to 1.9 ± 0.3 by 120mins, 1.8 ± 0.4 at 240mins with an increase to 2.1 ± 0.5 post dialysis (see Figure 4.6). The difference was statistically significant when comparing baseline segmental %SF_[Overall] to that at 120mins and 240mins ($p < 0.05$) but did not reach significance on comparing %SF_[Overall] at 120mins, 240mins ($p = 0.34$) and at recovery. There was a

statistically significant fall in the mean segmental %SF_[RRWM] from 2.7 ± 1.1 at baseline, 1.9 ± 0.7 at 120mins, 1.4 ± 0.6 at 240mins, and 2.2 ± 0.7 at recovery ($p < 0.05$) (see Figure 4.7).

Figure 4.6: Differences in mean segmental percentage SF in those developing RRWM

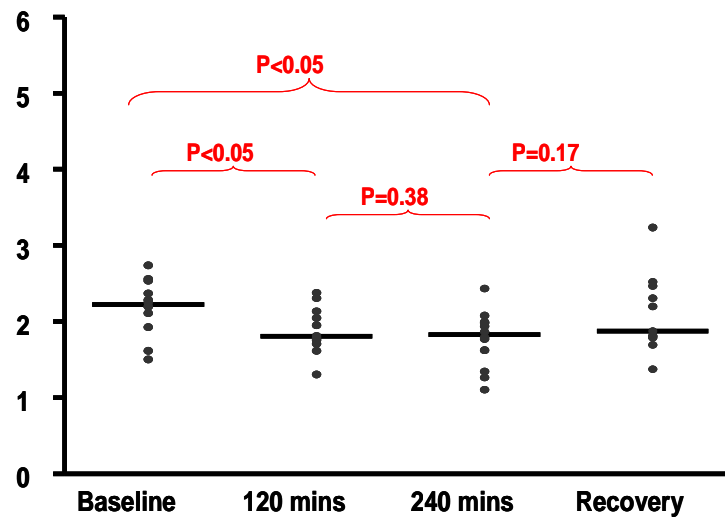
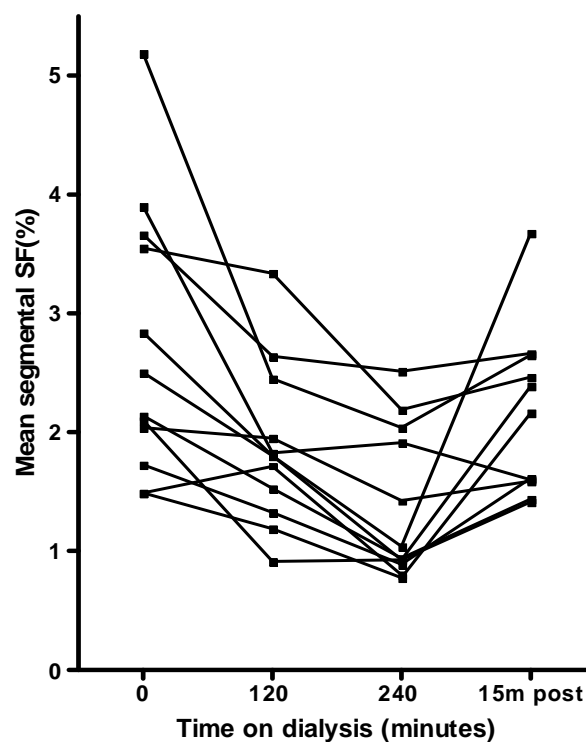
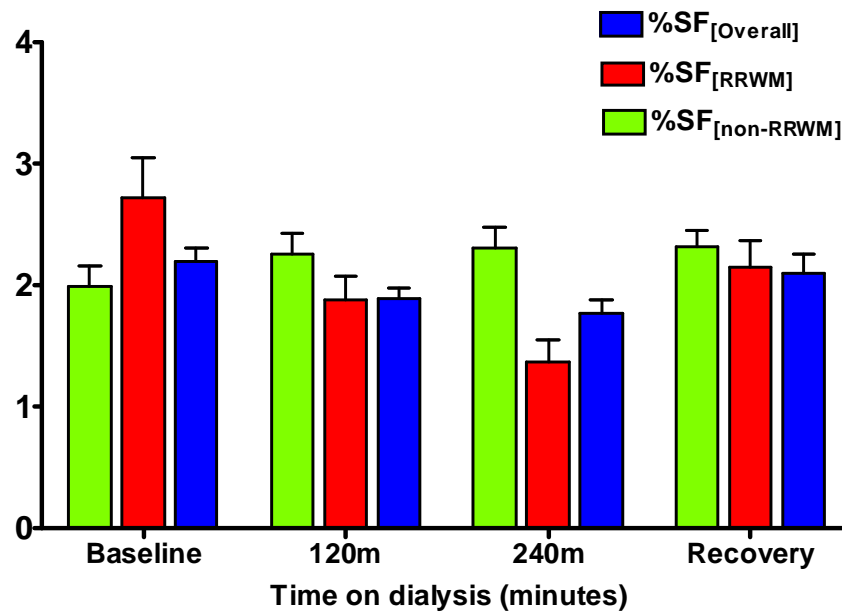


Figure 4.7: Mean segmental percentage SF in those developing RRWM



10/12 patients showed evidence of resolution of RRWM on recovery, as early as 15mins after completing dialysis (see Figure 4.8). The mean segmental $\%SF_{[nonRRWM]}$ increased from baseline to 240mins, 2.0 ± 0.6 to 2.3 ± 0.6 but did not reach statistical significance ($p=0.07$) (see Figure 4.8). The mean segmental $\%SF$ in the segments that developed RRWM was higher at baseline compared with those that did not (2.35 ± 0.52 versus 1.98 ± 0.63) (see Figure 4.8).

Figure 4.8: Mean Segmental Percentage Shortening Fraction Relative to Time On HD



- Significant difference between $\%SF_{[Overall]}$ {baseline v 120m}
- and {baseline v 240m} ($p<0.05$)

† Significant difference between $\%SF_{[RRWM]}$ {baseline v 120m}, {baseline v 240m}, {120m v 240m} and {240m v recovery} ($p<0.05$)

‡ In the remaining groups the difference was not statistically significant

This pattern of dialysis induced segmental RRWM is consistent with the definition of myocardial stunning. Pictorial representation of serial regional wall motion assessment from 2 patients illustrates the transient regional myocardial dysfunction that is seen during a HD treatment (see Figures 4.9 and 4.10).

Figure 4.9: Serial regional wall motion assessment from Patient 7 during HD

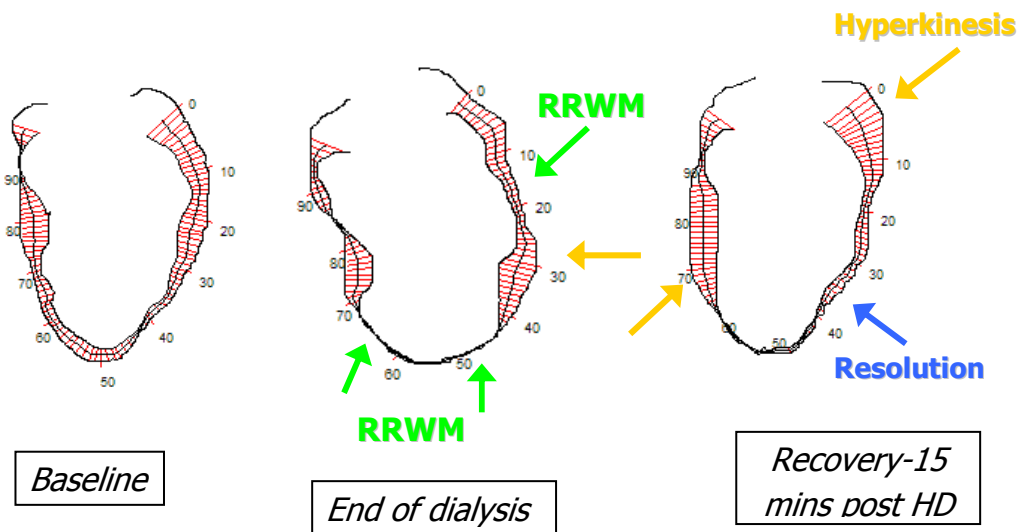
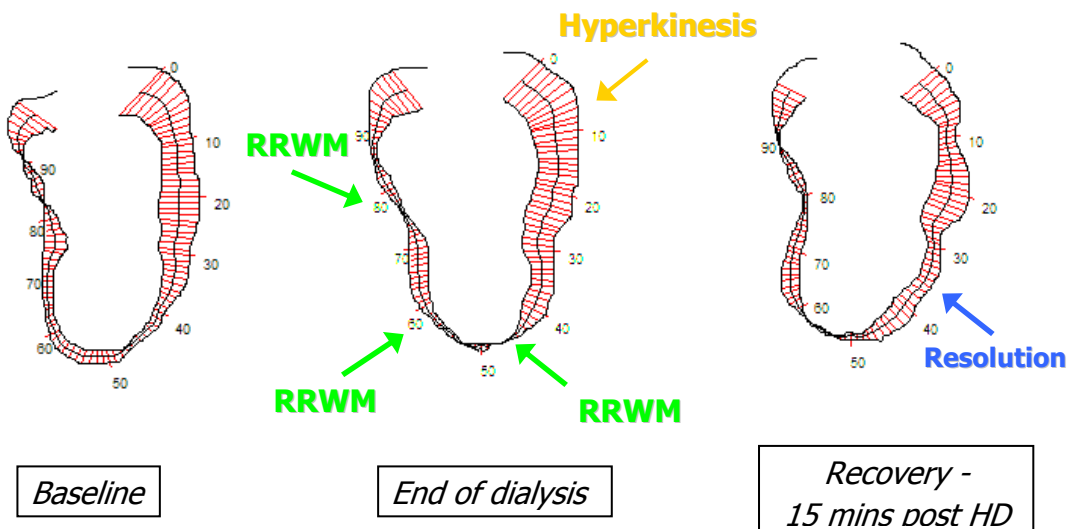


Figure 4.10: Serial regional wall motion assessment from Patient 9 during HD



Factors Associated With The Development Of Myocardial Stunning

The median intradialytic systolic BP fall for the group was 25 mmHg (range 6-90mmHg) and the lowest intradialytic systolic dialysis BP ranged from 58 to 110mmHg. A strong correlation was seen between intradialytic systolic BP change and mean segmental %SF_[RRWM] ($r = 0.56$, $p < 0.05$) as shown on figure 4.11. Similarly on univariate linear regression analysis there was a significant association between intradialytic systolic BP changes and mean segmental %SF_[RRWM] ($p < 0.05$), but not against lowest intradialytic systolic BP ($p = 0.68$).

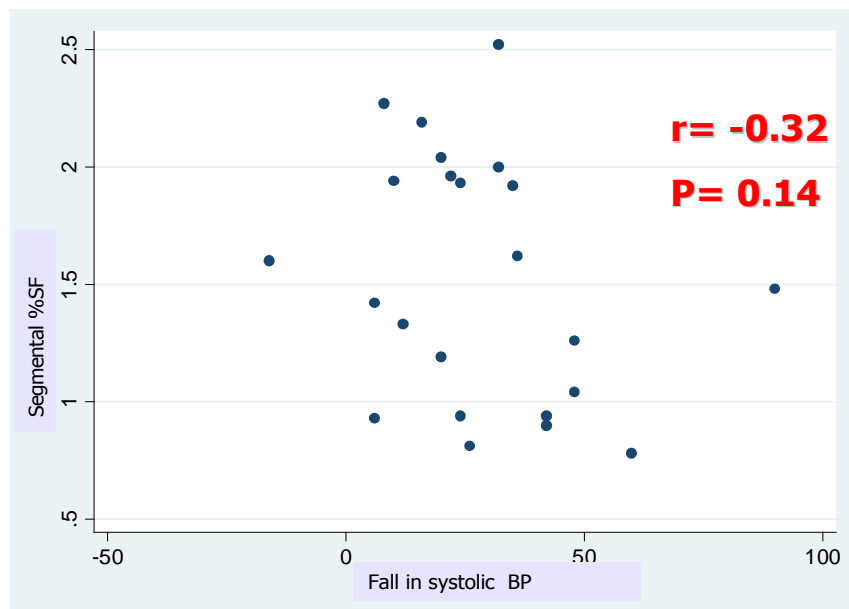


Figure 4.11: Graph of intradialytic blood pressure change and LV mean segmental shortening fraction

The median UF volume for the group was 29.4mls/kg (range 2-94mls/kg), and in one patient no UF was attempted. There was no significant association between UF volume and the number of segments that developed RRWM, or the mean segmental %SF_[RRWM]. Likewise on univariate linear regression analysis there was no association between UF volumes and mean segmental %SF_[RRWM] ($p = 0.6$). When considering both intradialytic

BP change and UF against the mean segmental %SF_[RRWM] the relationship between intradialytic BP change and the mean segmental %SF_[RRWM] disappeared (p=0.24). In this patient group UF volume correlated with change in BP during HD (r=0.56, p<0.05) as shown in Figure 4.12. Similarly on univariate linear regression there was a significant association between systolic BP change and UF volume (p<0.05, r² 0.32).

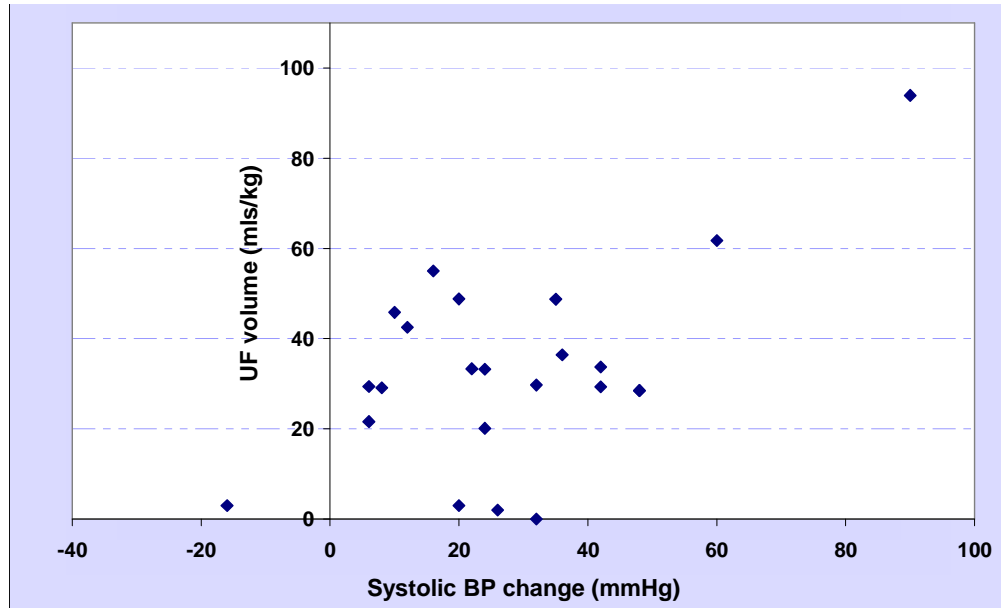


Figure 4.12: Graph illustrating the relationship between Systolic BP change and UF volume

I found no significant relationship between the number or intensity of RRWM as measured by the mean %SF_[RRWM] against patient age, dialysis vintage, pre-dialysis plasma urea levels, anaemia, LV mass, hsCRP or cTnI and the presence of a arteriovenous fistula. I could not test for the relationship between the absolute or change in heart rate during dialysis and RRWM as it was impossible to separate the tachycardic response that evolved as part of the haemodynamic response to HD and that as a direct result of the children, especially the infants, getting upset and crying during their echo assessments.

Hematological & Biochemical Profile & Markers of Cardiac Injury

The biochemical and hematological profile was typical of HD patients, showing a prevalence of anaemia (n= 5), hyperparathyroidism (n=7), hyperphosphataemia (n= 5) and acidosis (n=4). Routine laboratory values and dialysis adequacy are summarised in Table 4.2. Values for hsCRP exceeded 1µg/l in 6 patients post-dialysis and 3µg/l in one patient post-dialysis. In 8/12 patients the post-dialysis cardiac troponin I (cTnI) levels remained the same as pre-dialysis levels of <0.04µg/l. In the remaining 4 patients the cTnI levels increased post dialysis to up to 0.07µg/l (see Table 4.3).

Table 4.2: Biochemical and Haematological Profile

	Mean ± Standard Deviation	Range
Pre-dialysis Urea (mmol/l)	22.5 ± 4.2	15.2 to 28.2
Post-dialysis Urea (mmol/l)	4.5 ± 1.5	1.5 to 6.9
KT/V _{urea}	2.0 ± 0.5	0.5 to 3.1
URR (%)	80 ± 6	72 to 91
Haemoglobin (g/dl)	11.5 ± 1.4	9.1 to 13.1
Potassium (mmol/l)	5.3 ± 0.7	3.7 to 6.4
Phosphate (mmol/l)	1.5 ± 0.6	0.6 to 2.9
Albumin (g/l)	38.3 ± 2.5	34 to 41
PTH (pmol/l)	22.4 ± 22.9	0.3 to 89
Ionised Calcium (mmol/l)	1.2 ± 0.1	1.09 to 1.44
Bicarbonate (mmol/l)	23.9 ± 2.4	20 to 27
hs CRP (µg/l)	1.9 ± 1.5	0.4 to 5.5

URR: urea reduction rate

PTH: parathyroid hormone

hsCRP: highly sensitive C-reactive protein

Table 4.3: Cardiac Troponin I levels pre and post dialysis

Patient	Baseline cTNI ($\mu\text{g/l}$)	Post dialysis cTNI ($\mu\text{g/l}$)
1	<0.04	0.04
2	0.05	0.07
3	<0.04	0.04
4	<0.04	<0.04
5	<0.04	<0.04
6	<0.04	<0.04
7	<0.04	<0.04
8	<0.04	0.04
9	<0.04	<0.04
10	Not available	Not available
11	<0.04	<0.04
12	<0.04	<0.04

cTNI: Cardiac Troponin I

4.4.2

Speckle tracking two-dimensional strain assessment

For each patient speckle tracking 2D strain echo images were acquired during a single HD. However during the data analysis and thus assessment of peak strain and asynchrony three cardiac cycles were analysed per patient at each time point.

Peak Segmental Strain

Compared with age matched controls the peak segmental longitudinal strain was lower in uraemic patients at the start of dialysis. The difference was statistically significant in the baso-septal, mid-septal, mid-lateral and baso-lateral segments. During dialysis the peak longitudinal strain fell and the difference was statistically significant in all the segments (see Table 4.4).

There was no segmental difference in peak circumferential strain between the controls and uraemic patients pre-dialysis. During dialysis the peak circumferential strain fell and the difference was statistically significant in the lateral and posterior segments. The exception was the antero-septal segments in which the peak circumferential strain was significantly higher (see Table 4.5).

Segmental peak radial strain was lower in uraemic children pre-dialysis compared with age matched controls. The difference was statistically significant in the anterior, posterior, inferior and lateral segments. During dialysis the peak radial strain increased in all the segments but the difference only achieved statistical significance in the posterior segments (see Table 4.6).

Inter-segmental Synchronicity

The asynchrony index or standard deviation of time to peak strain over the 6 segments was significantly higher pre-dialysis compared with the controls and higher still post dialysis in all 3 axes. Similarly the maximum inter-segmental time difference to peak strain progressively increased from the age matched controls to uraemic patients pre-dialysis and higher still in the post dialysis patients. The difference was statistically significant in the longitudinal, circumferential and radial axes (see Table 4.4 to 4.6).

Figures 4.13 and 4.14 represent longitudinal time strain curves for patients 7 and 9, the same patients whose regional wall motion assessments were shown in Figures 4.9 and 4.10 earlier in this chapter. The longitudinal strain curves demonstrate a reduction in peak longitudinal strain post dialysis and variations in the time to peak strain between the 6 segments.

Table 4.4: LV segmental longitudinal strain

	Pre-dialysis Mean [95% CI]	Post-dialysis Mean [95% CI] §	Control Mean [95% CI] *
Peak basal-septal strain	-17.93 [-18.75 to -17.11]	-16.10 [-17.30 to -14.89] § $p<0.05$	-20.10 [-21.29 to -18.92] * $p<0.05$
Peak mid-septal strain	-19.01 [-19.73 to -18.30]	-17.35 [-18.22 to -16.47] § $p<0.05$	-21.40 [-22.27 to -20.53] * $p<0.05$
Peak apical-septal strain	-21.20 [-22.32 to -20.07]	-16.69 [-18.13 to -15.24] § $p<0.05$	-21.42 [-22.79 to -20.06] * $p=0.73$
Peak apical-lateral strain	-17.24 [-18.72 to -15.77]	-14.08 [-15.58 to -12.59] § $p<0.05$	-17.33 [-19.12 to -15.54] * $p=0.16$
Peak mid-lateral strain	-15.02 [-16.22 to -13.81]	-12.45 [-13.83 to -11.07] § $p<0.05$	-17.75 [-19.11 to -16.38] * $p<0.05$
Peak basal-lateral strain	-17.60 [-19.11 to -16.10]	-15.00 [-16.40 to -13.60] § $p<0.05$	-21.41 [-23.1 to -19.73] * $p<0.05$
Time of peak segmental strain [Inter-segmental time SD]	45.60 [41.43 to 49.77]	51.85 [44.53 to 59.16] § $p<0.05$	34.95 [29.45 to 40.46] * $p<0.05$
Time of peak segmental strain [Inter-segmental time difference]	108.02 msec [96.47 to 119.56]	129.22 msec [107.51 to 150.94] § $p<0.05$	81.07 msec [65.83 to 96.30] * $p<0.05$

§ Difference between pre- and post-dialysis patients

* Difference between pre-dialysis patients and controls

Table 4.5: LV segmental circumferential strain

	Pre-dialysis Mean [95% CI]	Post-dialysis Mean [95% CI] §	Control Mean [95% CI] *
Peak antero-septal strain	-25.75 [-28.55 to -22.95]	-27.93 [-30.64 to -25.23] § $p<0.05$	-24.75 [-27.78 to -21.71] * $p=0.63$
Peak anterior strain	-22.00 [-24.30 to -19.70]	-20.75 [-22.94 to -18.58] § $p=0.20$	-20.50 [-22.84 to -18.16] * $p=0.24$
Peak lateral strain	-17.54 [-19.99 to -15.10]	-12.24 [-13.88 to -10.59] § $p<0.05$	-17.35 [-19.99 to -14.70] * $p=0.37$
Peak posterior strain	-12.92 [-15.62 to -10.22]	-12.63 [-15.47 to -9.78] § $p<0.05$	-14.23 [-16.77 to -11.69] * $p=0.27$
Peak inferior strain	-16.99 [-19.04 to -14.95]	-16.75 [-18.67 to -14.82] § $p=0.21$	-17.79 [-20.66 to -14.92] * $p=0.64$
Peak septal strain	-23.45 [-25.22 to -21.67]	-23.15 [-25.39 to -20.91] § $p=0.31$	-22.65 [-26.72 to -18.59] * $p=0.71$
Time of peak segmental strain [Inter-segmental time SD]	63.02 [50.64 to 75.39]	55.95 [47.90 to 64.00] § $p<0.05$	35.34 [28.10 to 42.58] * $p<0.05$
Time of peak segmental strain [Inter-segmental time difference]	164.27 msec [125.49 to 203.06]	138.12 msec [117.49 to 158.75] § $p<0.05$	84.41 msec [64.82 to 103.99] * $p<0.05$

§ Difference between pre- and post-dialysis patients

* Difference between pre-dialysis patients and controls

Table 4.6: LV segmental radial strain

	Pre-dialysis Mean [95% CI]	Post-dialysis Mean [95% CI] §	Control Mean [95% CI] *
Peak antero-septal strain	36.16 [30.36 to 41.96]	47.81 [35.99 to 59.62] § $p=0.13$	43.44 [36.27 to 50.62] * $p=0.11$
Peak anterior strain	41.13 [34.32 to 47.93]	45.11 [39.12 to 51.10] § $p= 0..88$	54.57 [47.21 to 61.93] * $p<0.05$
Peak lateral strain	46.50 [37.82 to 55.18]	46.93 [40.58 to 53.28] § $p=0.07$	62.20 [55.29 to 69.11] * $p<0.05$
Peak posterior strain	45.25 [36.64 to 53.86]	47.17 [40.24 to 54.10] § $p<0.05$	63.15 [55.83 to 70.47] * $p<0.05$
Peak inferior strain	40.78 [34.39 to 47.12]	44.56 [37.74 to 51.37] § $p= 0.2$	55.59 [47.01 to 64.16] * $p<0.05$
Peak septal strain	36.04 [30.46 to 41.63]	41.57 [35.33 to 47.82] § $p=0.08$	43.37 [35.41 to 51.33] * $p=0.12$
Time of peak segmental strain [Inter-segmental time SD]	34.94 [25.79 to 44.09]	35.09 [25.14 to 45.04] § $p=0.05$	22.07 [15.27 to 28.86] * $p<0.05$
Time of peak segmental strain [Inter-segmental time difference]	81.59 msecs [58.72 to 104.46]	79.07 msecs [53.75 to 104.39] § $p<0.05$	48.43 msecs [32.22 to 64.64] * $p<0.05$

§ Difference between pre- and post-dialysis patients

* Difference between pre-dialysis patients and controls

Figure 4.13: Longitudinal time strain curves for patient 7. The top panel is pre-dialysis and the lower panel post dialysis.

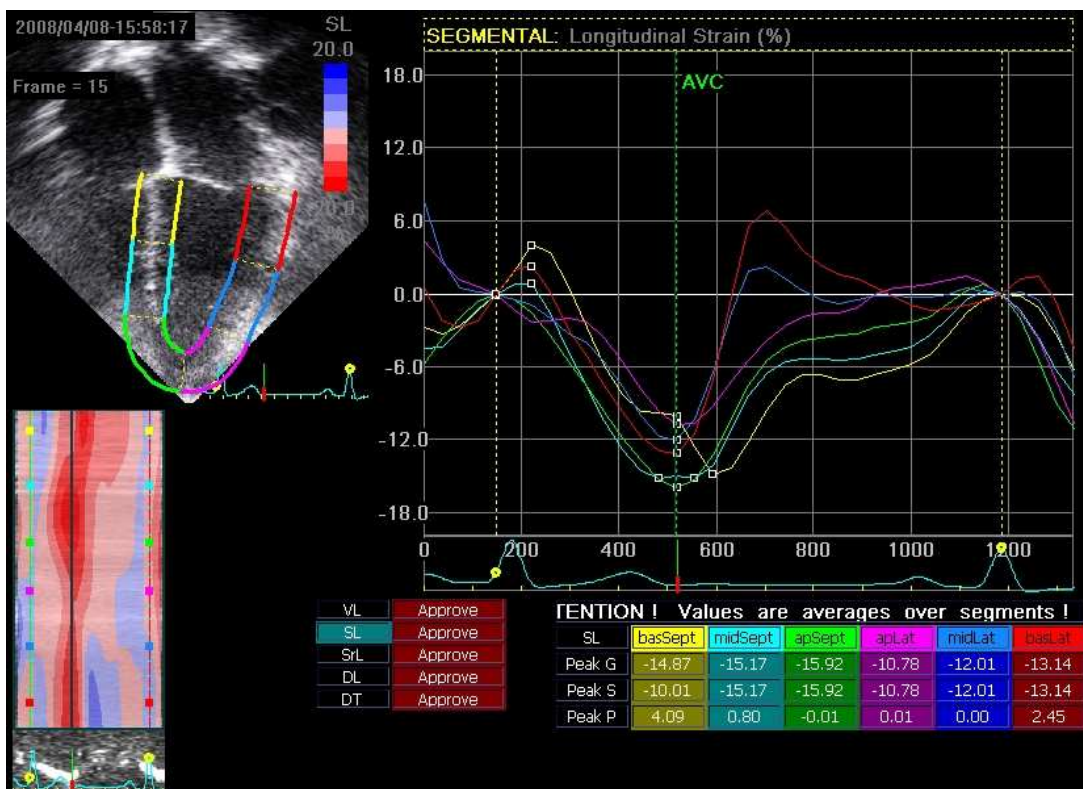
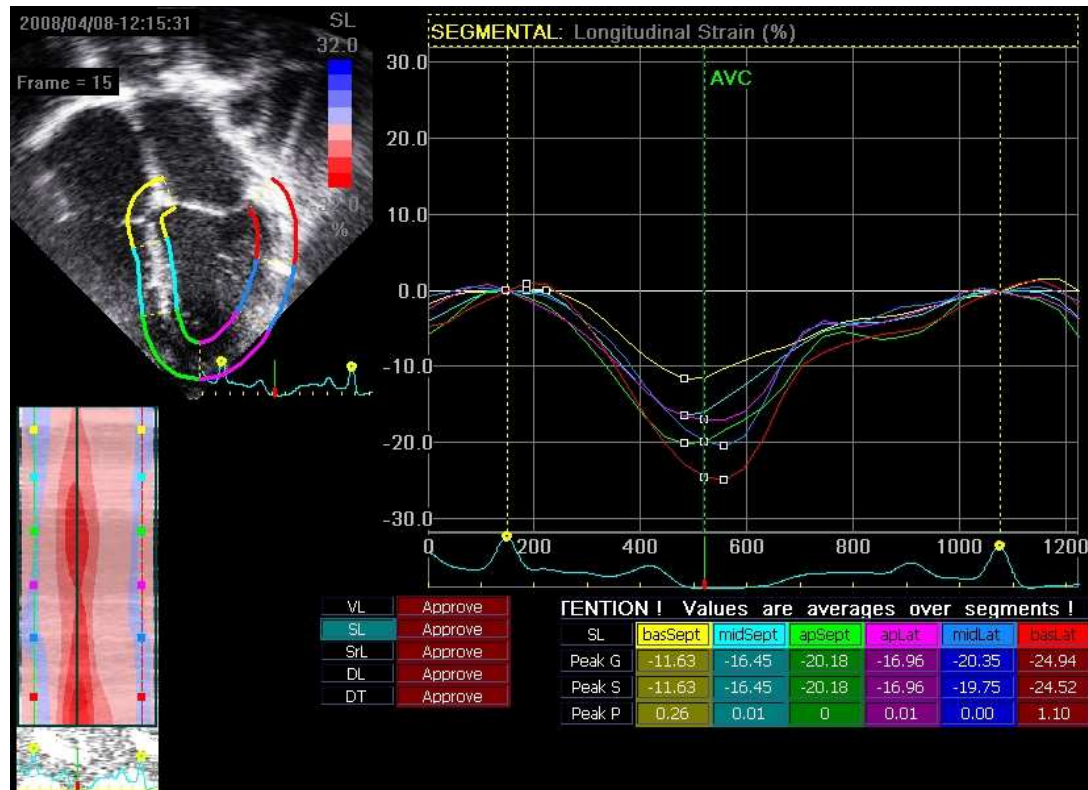
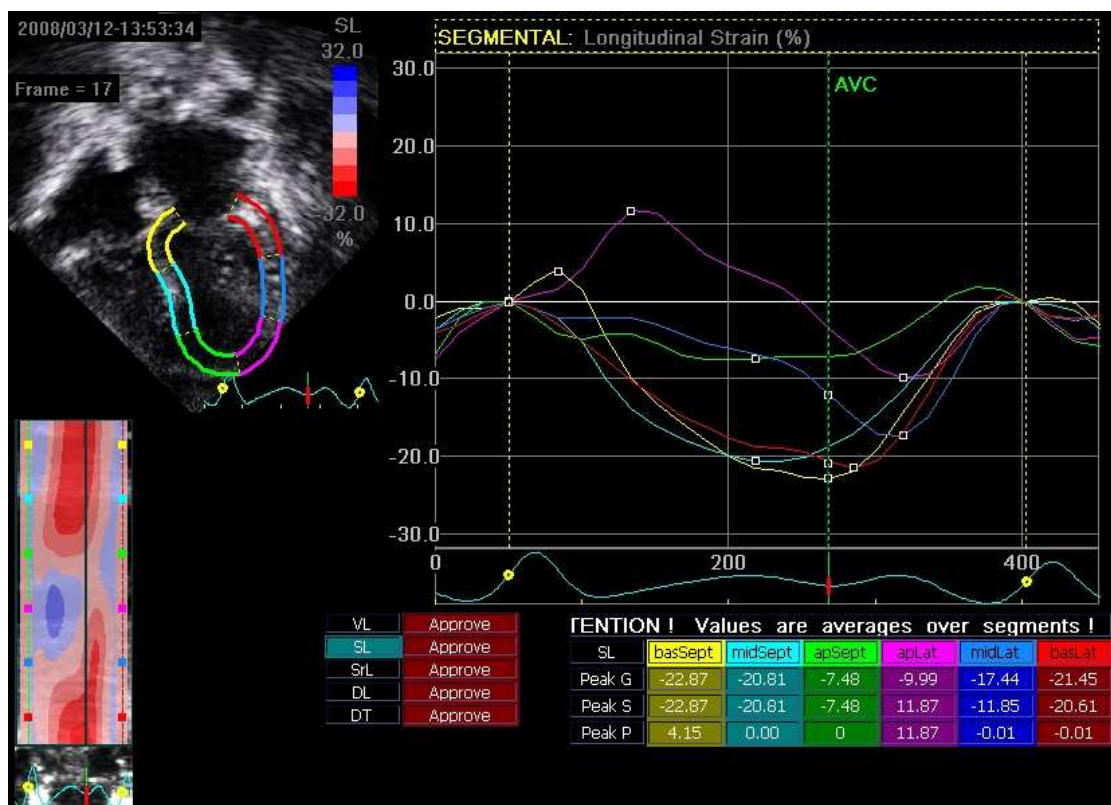
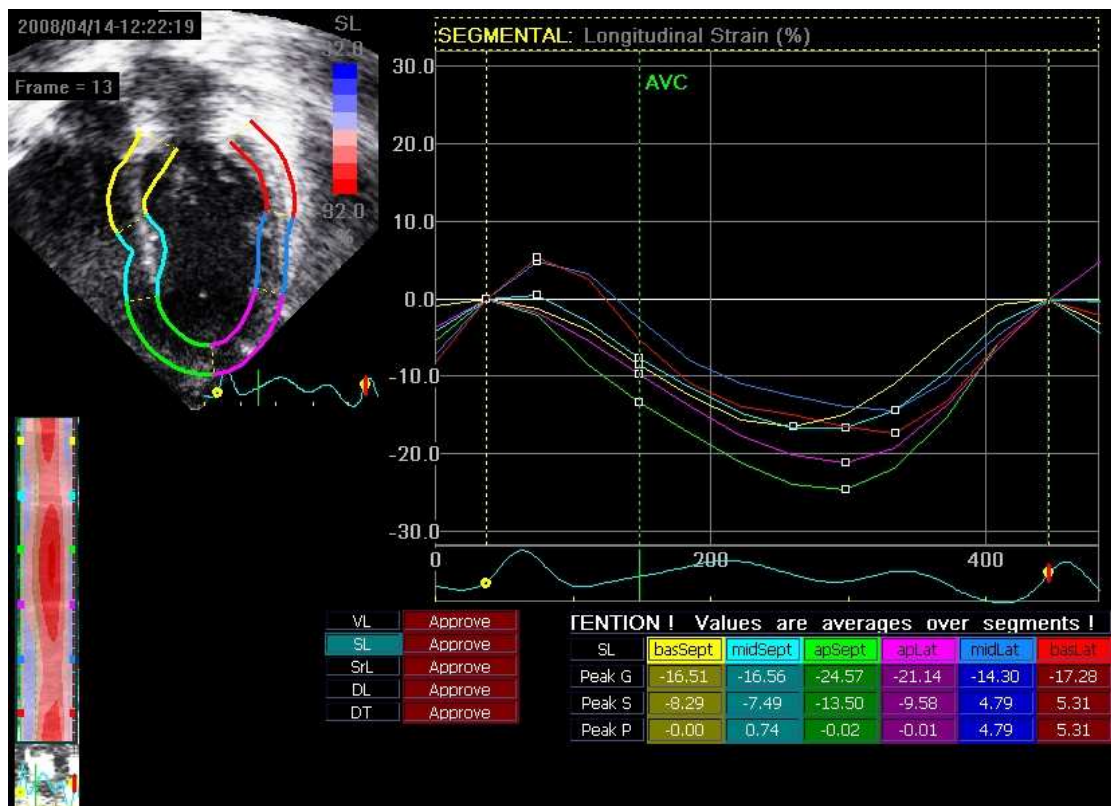


Figure 4.14: Longitudinal time strain curves for patient 9. The top panel is pre-dialysis and the lower panel post dialysis.



Factors Associated with Strain Reduction

Intradialytic peak longitudinal strain reduction was significantly associated with systolic BP, change in systolic BP during dialysis and the UF volume (see Table 4.7). During HD neither peak circumferential nor peak radial strain reductions were found to be significantly associated with intradialytic BP, UF volumes or dialysis vintage (see Tables 4.8 and 4.9).

Table 4.7: Factors associated with peak longitudinal strain reduction during HD

	Pearson's Correlation	R ²	p-value	Logistical Regression Coefficient	p-value
Absolute systolic BP	-0.26	0.07	p<0.05	0.22	0.41
Intradialytic systolic BP change	0.317	0.10	p<0.05	-0.18	0.54
UF (mls/kg)	0.30	0.09	p<0.05	0.09	0.76
Months on HD	0.05	0.002	p=0.71	0.13	0.80

Table 4.8: Factors associated with peak circumferential strain reduction during HD

	Pearson's Correlation	R ²	p-value	Logistical Regression Coefficient	p-value
Absolute systolic BP	0.20	0.04	p=0.18	0.04	0.9
Intradialytic systolic BP change	-0.03	0.001	p=0.87	-0.09	0.71
UF (mls/kg)	0.14	0.02	p=0.34	0.04	0.9
Months on HD	-0.26	0.07	p=0.09	-0.88	0.13

Table 4.9: Factors associated with peak radial strain reduction during HD

	Pearson's Correlation	R ²	p-value	Logistical Regression Coefficient	p-value
Absolute systolic BP	0.07	0.005	p=0.73	0.03	0.89
Intradialytic systolic BP change	-0.15	0.02	p=0.44	0.18	0.28
UF (mls/kg)	-0.22	0.05	p=0.91	0.05	0.81
Months on HD	-0.08	0.006	p=0.70	0.16	0.72

Predictors of Intradialytic Systolic BP

Within the cohort of 15 patients the UF volume ranged from 3mls/kg/hr to 86mls/kg/hr. The lowest documented intradialytic systolic BP ranged from 58mmHg to 140mmHg. On univariate linear regression analyses percentage strain reduction was not predictive of intradialytic BP (see Table 4.10).

Table 4.10: Predictors of intradialytic systolic BP

	Correlation Coefficient	Significance
% Reduction in peak longitudinal strain during HD	0.42	p=0.19
% Reduction in peak circumferential strain during HD	0.19	p= 0.52
% Reduction in peak radial strain during HD	0.03	p=0.91

The intradialytic systolic BP reduction ranged from 6mmHg to 90mmHg. On univariate linear regression analyses both the percentage reduction in longitudinal strain and radial strain were significantly predictive of intradialytic systolic BP fall (see Table 4.11). Percentage reduction in longitudinal strain showed a positive correlation but radial strain showed a negative correlation, namely a greater fall in BP is seen in patients where peak radial strain shows little change during dialysis.

Table 4.11: Predictors of intradialytic systolic BP fall

	Correlation Coefficient	Significance
% Reduction in peak longitudinal strain during HD	0.66	p<0.05
% Reduction in peak circumferential strain during HD	-0.32	p=0.19
% Rise in peak radial strain during HD	-0.70	P<0.05

4.5 Discussion

The prevalence of myocardial stunning in patients with CAD is high, cumulative and associated with an attendant risk of increased CV events and mortality. The same phenomenon has now been demonstrated in prevalent adult dialysis patients¹¹⁷ and ‘low risk’ non-diabetic, non-cardiac adult HD patients⁶⁸ but until now there has been no evaluation of the risk in children. Compared with age matched controls I have demonstrated altered baseline myocardial function in uraemic children aged between 1 to 17 years. During conventional 4 hour HD the myocardial function deteriorates further with biochemical evidence of ischaemic injury. The effect is global across all segments as opposed to a segmental distribution specific to an isolated coronary artery. The adverse impact on myocardial fibres within the LV wall is however specific with a predisposition to LV longitudinal shortening. The degree of myocardial dysfunction is associated with intradialytic blood pressure change and UF volumes. Nonetheless owing to an early compensatory hyperkinetic response in regions of the LV, preservation of circumferential shortening and increased radial thickening, the global LVEF did not fall, but arguably neither did it rise as one would expect following a significant hemodynamic challenge.

Left ventricular contraction relies on the co-ordinated shortening action of myocardial fibres in multiple directions: longitudinal shortening, radial thickening and circumferential shortening combined with torsion of the heart. The alignment of heart fibres and resultant patterns of regional strain is heterogeneous. The coronary blood supply to segments of the heart also shows significant variation. In this study regional wall motion assessment (RWMA) demonstrated significant dialysis induced regional myocardial dysfunction with preponderance for basal and apical segments. The strain analyses showed a reduction in peak strain but the difference was only significant in the longitudinal axis and all the segments were involved. With this discrepancy in segmental involvement there is an implication that 2D strain may be more sensitive measure than wall motion of mild segmental LV dysfunction. RWMA assessment is primarily an assessment in the longitudinal axis and uses the inward motion of endocardial borders as the sole marker of abnormal contraction. However the visual estimation of wall motion can be very subjective and does not take into account wall thickening, twisting or transmural heterogeneity. In contrast 2D speckle tracking provides a multi-axis assessment of LV function employing functional components that are not visible to the naked eye. The motion of myocardial tissue is measured indirectly by the motion pattern of speckles tracking along the direction of the wall, not along the ultrasound beam. This makes it both translation and angle independent with lower inter and intra-operator variability compared with RWMA¹³¹. Furthermore in a direct comparison of the two, assessments of wall motion cannot differentiate between active and passive movement of a myocardial segment whereas deformation has the ability to discriminate. In the heart this is particularly important as ventricular wall motion is position dependent. As the apical parts of the ventricle pull down the ventricular base, the wall motion increases from apex to base and thus some of the measured wall motion

effect in the base is the combined effect of contraction and also apical tethering. Thus even completely passive segments can show motion but not deformation. 2D speckle tracking is a novel method for assessing regional myocardial function with minimal experience in children. In adults however myocardial strain quantification has been validated against tagged cardiac magnetic resonance imaging¹³⁵ and has been shown to be accurate and it is fast becoming the tool of choice in evaluating patients prior to cardiac resynchronisation, differentiating between hibernating myocardium and infarcted myocardium. My limited experience in children was very positive and parallels these reports in adults.

Longitudinally directed fibres are mainly located in the subepicardium and subendocardium regions of the LV. They only form a small proportion of the total ventricular myocardial mass but play a major role in the maintenance of normal ejection fraction. I found a selective reduction in longitudinal strain during HD. In simple terms this can be explained away by the heterogeneity of the heart architecture, however the apparent vulnerability of longitudinal shortening is not too dissimilar to other disease states and therefore unlikely to be either a coincidence or a normal variation. A degree of long-axis systolic dysfunction has been frequently reported in conjunction with diastolic dysfunction¹³⁶. Regional reduction in the extent and velocity of long axis shortening has been shown to be a sensitive and specific finding after myocardial infarction^{137, 138}. In hypertensive patients LV long axis function abnormalities have been found to present even before the onset of hypertension, but circumferential fractional shortening remain unchanged¹³⁷. Both hypertension and diastolic dysfunction are features common to children on dialysis^{22, 27, 139} and their presence may in part be

responsible for the findings or they share a common pathogenic pathway for longitudinal axis dysfunction dominance.

One feature that distinguishes children from adults is the absence of significant epicardial atheromatous CAD. They do however share a high prevalence of risk factors for adult-type cardiovascular disease that have been associated with a reduced coronary flow reserve and thus a propensity to demand ischaemia¹⁴⁰. Of these, hypertension, anaemia, hyperparathyroidism and hyperphosphataemia were significantly prevalent in these patients. Children can also display a constellation of altered functional and morphological cardiovascular features that predisposes them to ischaemic insults. LVH for example progresses to maladaptive cardiac remodeling characterized by decreased capillary density, subendothelial perfusion¹⁴¹ and decreased coronary contractile reserve¹⁴². Overt LVH was present in one patient and borderline hypertrophy in another 3 patients. 5/17 of the patients were common to a study conducted by Shroff et al.¹¹⁹ reporting findings of diminished arterial wall compliance and coronary and carotid artery calcification. Such vascular abnormalities are accepted markers of asymptomatic arteriosclerosis and mortality¹⁴³ and perhaps indicative of coronary microcirculation abnormalities. Evidence for inappropriately raised sympathetic nerve activity in dialysis patients¹¹⁸ raises the possibility of an alternative explanation for the regional LV dysfunction, namely takotsubo or 'stress' cardiomyopathy¹⁴⁴. However Dasselaar et al demonstrated a fall in regional and global myocardial blood flow, 30 minutes into a HD session, in the absence of UF that preceded regional LV dysfunction⁶⁸. This is the inverse of the causal sequence of takotsubo or 'stress' cardiomyopathy. In addition the children showed no evidence of apical ballooning, a feature typical of classical takotsubo cardiomyopathy. Nevertheless the effects of raised sympathetic nerve activity

may be relevant by mediating microvasculature derangement and vasospasm. I found no significant association between biochemical and cardiac risk factors and the severity of myocardial stunning. This is most likely due to the fact cardio-renal performance is influenced by a number of humoral and genetic factors¹⁴⁵ that act collectively to exert an effect but in isolation, particularly in paediatrics, are too small to be detectable from our sample size.

The major determinant of intradialytic BP is cardiac output and end diastolic volume¹⁴⁶ but clearly regional LV function is important as evidenced by reports of reduced haemodynamic stability in patients developing myocardial stunning despite below average UF volumes¹²⁹. Shoji et al found BP reduction during dialysis and not hypertension in adult HD patients as a factor that influenced survival negatively¹⁴⁷. I found the UF volume and both the reduction and absolute intradialytic systolic BP to be related to dialysis induced longitudinal axis LV dysfunction, but only reduction in systolic BP was significantly associated with abnormalities in regional wall motion. These differences are most likely related to technique differences. 2D speckle tracking is slowly gaining credence over RWMA with improved accuracy and reproducibility qualities. It also has the ability to detect subtle and milder abnormalities in regional LV dysfunction, particularly those secondary to ischaemia, and thus even weak correlations became more apparent. Peak segmental strain was not predictive of absolute systolic BP but percentage changes in LV longitudinal shortening and radial thickening were both found to be predictive of intradialytic blood pressure changes. The implication is that actual BP is not as important as the failure to maintain BP in initiating and propagating myocardial stunning during dialysis. Children appear to be different to adults, with a more direct relationship between BP and UF volumes. In addition, as a consequence of

residual renal function, some exist closer to their dry weight and are thus very sensitive to fluid shifts during dialysis. Combined with a poorly compliant left ventricle²⁷ and peripheral conduit vessels^{32, 33}, abnormal vascular tone, UF mediates a reduction in cardiac output and BP. In the face of an attenuated coronary reserve, ischemia prevails when the hemodynamic demand of HD is not met by an adequate increase in myocardial blood flow.

There is considerable evidence alluding to the value of both CRP³⁹ and baseline cardiac troponin as markers of cardiovascular disease and mortality in ESRD. An acute rise in cardiac troponin levels in HD patients is also indicative of sub-clinical myocardial ischaemic injury^{58, 59, 63}. I found elevated levels of high sensitivity CRP in half of the dialysis patients that were tested and a rise in cardiac Troponin I (cTnI) levels in 25%. Elevated plasma cardiac troponins levels are usually only seen 6-12 hours after the acute injury. However in this study post-dialysis plasma samples were taken 15minutes after the end of the HD session and this may explain my failure to demonstrate a rise in cardiac troponin I levels in more of the patients. In the patients that did demonstrate a rise in plasma cardiac enzymes levels it is conceivable that the cardiac insult occurred early in the 4hour HD session and thus levels were detectable post-dialysis. An earlier, alternative marker of cardiac injury is mechanical synchronisation of LV contraction. Dssynchronous left ventricular long axis function is common in patients with chronic stable coronary artery disease¹³⁶. In fact the presence and localisation of asynchrony correlates closely with reversible abnormalities on thallium myocardial perfusion scanning¹³⁸ and precedes ECG changes or symptoms and changes in myocardial systolic amplitude of motion. Asynchrony is believed to a sensitive and earlier marker of ischaemia¹⁴⁸. I observed an exaggerated dssynchrony index in longitudinal,

circumferential shortening and radial thickening at the end of HD. This may reflect ischaemic injury that was detected earlier than more traditional biochemical markers of cardiac injury. Within this context it has the potential for becoming very useful in the clinical environment in identifying ‘at risk’ patients.

4.6 Study Limitations

This was a preliminary study looking at regional LV dysfunction in children on HD and the sample size was small. Nevertheless the study was adequately powered for the primary outcome. RWMA and analysis was repeated twice in the same patient and the results showed concordance in the localization of abnormalities but the number of segments involved differed. This may indicate poor reproducibility or conversely is the consequence of differences in intra-patient UF volumes and intradialytic hemodynamic parameters between treatments. 2D speckle tracking analyses of the same patients were again consistent with findings from RWMA but the prevalence of segmental myocardial dysfunction was higher. This is likely to be due to the fact that 2D speckle tracking screened LV function in 3 axes and the assessment incorporated an additional parameter, dyssynchrony index, and was thus a more sensitive test.

I have already alluded to the limitations of RWMA. However looking specifically within the context of children, 2D speckle analyses are also at risk of inaccuracy. Normally, the resting heart rate is influenced by the age of the child and the younger the child the higher their resting heart rate. During dialysis patients become tachycardic. The optimal frame rate for speckle tracking seems to be 50–70 frames per second, however in the face of tachycardia this could result in under sampling. In an attempt to manage this problem I tried to use higher frame rates but this resulted in a reduction of

spatial resolution and in some patients this had to be abandoned as a result of less than optimal speckle tracking. In essence neither assessment is perfect but the gold standard for assessing functional change, magnetic resonance imaging, is technically impossible in patients while they are receiving HD. Of the two assessments speckle tracking shows more promise in detecting regional LV function, however prior to recommending it for general application 2D speckle tracking use must be validated in children.

In this study I have made two assumptions. Firstly, having extrapolated from adult data, I have implied that HD in children is also associated with reduced myocardial blood flow. I have also assumed based both on negative findings or the absence of reports in the literature that none of the children in the cohort had significant epicardial CAD. Both of these questions could have been answered by subjecting the children to angiography or perfusion imaging but I elected not to do this due to the practical implications and severe reluctance from both the patients and dialysis nurses. Of the two, perfusion imaging may be considered to be less invasive, however adult data suggests that myocardial scintigraphy is imperfect in detecting CAD in patients with ESRD [De Lima JJ,03] and indeed doubts about applicability in patients with more severe CKD has led to renal disease currently not being categorised in the most recent 'Appropriateness Criteria for Stress Echocardiography' recommendations¹⁴⁹.

4.7 Conclusion

I have shown for the first time that paediatric patients receiving conventional HD suffer from dialysis induced myocardial stunning. As in adults, this reflects the degree of HD induced haemodynamic instability. This data, in combination with previous adult

studies suggest that even in the absence of conventional epicardial coronary artery disease the characteristic cardiovascular phenotype in uraemic HD patients is severe enough to limit the microvasculature response to haemodynamic stress and predisposes to significant demand myocardial ischemia.

Myocardial stunning is progressive with raised attendant mortality. In any serious attempt to modify the cardiovascular burden in dialysis patients we will require an accurate method for detecting ischaemic myocardial injury. In my limited experience the novel method of 2D speckle tracking was superior to the traditional method of regional wall motion assessment as it is able to offer a more comprehensive assessment of LV function combined with the possibility of detecting ischaemic myocardial injury in its early stages.

Chapter Five

Moderators of Intradialytic Morbidity

5.1 Hypotheses

- Manipulating the HD prescription can improve intradialytic morbidity during paediatric dialysis
- The use of sodium and UF profiles improves cardiovascular stability
- The prescribing of intradialytic mannitol reduces the frequency and severity of intradialytic symptoms
- The application of sequential dialysis during the course of the dialysis treatment improves the UF potential

5.2 Introduction

The development of intradialytic symptoms and hypotension can result in premature discontinuation of treatment and delivery of sub-optimal dialysis with an attendant adverse impact on health¹⁵⁰. Broadly speaking dialysis failure (in the absence of clotting the extracorporeal circuit) has two aetiologies, dialysis dysequilibrium and UF mediated cardiovascular decompensation. The challenge is that during an acute episode symptoms can be non-discriminatory and their pathophysiological mechanisms obscure. Thus developing strategies to prevent or manage dialysis failure is both difficult and may have variable results. The recognised measures for improving haemodynamic stability during HD, such as avoiding food during dialysis¹⁵¹ and treating intradialytic hypocalcaemia¹⁶ are of limited value. Experience with newer methods such as sodium and UF profiles⁷⁸ and intradialytic mannitol are inconsistent and limited in paediatrics.

5.3 Subjects and Methods

5.3.1 Prevalent chronic HD patients

I developed a standardized practice for prescribing chronic HD at the Hospital for Sick Children, Toronto. After 8 months the data from these dialysis treatments was collected and analysed. I included all children on HD for a minimum of one month, excluding those patients receiving nocturnal HD and those that were acutely unwell and/or in the paediatric intensive care unit. Ethics approval for this study was granted by the local research ethics board and informed consent was obtained from patients or their guardians.

Patients

Baseline characteristics of the patients and dialytic treatments are listed in Table 5.1. A total of 11 patients were studied, 5 female and 6 male. The underlying renal disease was focal segmental glomerulosclerosis (1 patient), autosomal recessive polycystic kidney disease (1 patient), renal dysplasia (4 patients), chronic drug toxicity and BK virus nephropathy secondary to cardiac transplant (1 patient), membranous glomerulonephritis (1 patient), ANCA negative glomerulonephritis (1 patient), unknown (2 patients). 5/11 patients were polyuric (daily urine output >1.5mls/kg/hr); one had panhypopituitarism; one had a chronic history of intradialytic cramping; one had been treated with a second heart transplant and had evidence of significant right ventricular dilatation on a peak dobutamine stress test but normal right and left ventricular function at rest. The resting heart rate was no different between the cardiac transplant patients and the remaining patients. Throughout the observation period 6 patients were normotensive without medication, 2 patients were on one antihypertensive

and 3 patients were on two antihypertensives. 3/11 patients had evidence of ventricular or septal hypertrophy.

Table 5.1: Baseline characteristics of patients and their dialytic treatments

Sex (M/F)	5/5
Age (years)	12.8 \pm 2.93
Dry weight (kg)	40.2 \pm 15.6
Urine output (yes/no)	5/5
Urine output (mls/kg/hr)	1.61 \pm 0.81
Pre-dialysis plasma haemoglobin (g/l)	94.8 \pm 11.9
Pre-dialysis plasma albumin (g/l)	35.8 \pm 4.63
Pre-dialysis plasma ionised calcium (mmol/l)	1.24 \pm 0.16
Mean gross UF (mls/session)	1475 \pm 937
Mean gross UF (%body weight /session)	4.77 \pm 2.09
Blood flow rate (mls/min)	120-350
Dialysate flow rate (mls/min)	200-650
Kt/V	1.71 \pm 0.27
Mean Systolic BP at the start of dialysis (mmHg)	113 \pm 20.5
Mean Diastolic BP at the start of dialysis (mmHg)	68.1 \pm 12.3
Mean Heart rate at the start of dialysis (beats/min)	100 \pm 19.2

The Standardised HD Prescription

All patients were dialysed using the Fresenius 2008K® or 2008H®. Patients received HD for 3hrs, 4 times per week or for 4hrs, 3 times per week. All dialysis membranes were high flux, triacetate cellulose or polysulfone membranes. Dialysis flow rates varied between 200 to 650mls/min but were kept constant by a dialysate to blood flow ratio of 2 to 2.5. Blood flow rates were calculated to provide an estimated urea clearance of 4mls/kg/min. The dialysis prescription was adjusted monthly to achieve a

urea reduction ratio between 65 to 80% and Kt/V urea between 1.2 and 1.6 (calculated from Daugiradas single pool kinetics)¹¹⁵. All patients received heparin as standard anticoagulation or no heparin if they were at a risk of bleeding. Patients were dialysed against 35mmol/l bicarbonate, 1.25mmol/l calcium, with a small quantity of acetate in the acidic component to stabilise the dialysate. The dialysate temperatures were set at constant value of 37.5°C. Patients were permitted to consume one meal during the first hour of their treatment. Mannitol was given if the pre-dialysis plasma urea concentration was greater than 35mmol/l or if the patient experienced symptoms suggestive of dialysis dysequilibrium (severe headaches or altered levels of consciousness) on at least two separate occasions during previous dialysis treatments. For these patients 1g/kg mannitol was administered intravenously during the first hour of the first weekly dialysis session or 0.5g/kg during two dialysis sessions per week.

UF Profiles

The prescribed UF rate was determined from the interdialytic weight gain plus the volume of fluid given during the dialysis treatment including priming fluid, blood products and nutrition. Pre-programmed Fresenius 2008K UF profile patterns outlined in Figure 5.1 were used (when the Fresenius 2008H machine was used the UF profiles were adjusted to match those on the 2008K model). As shown profile 3 was a decreasing step pattern, profile 6 an alternating high/low UF rate and profile 2 a decreasing linear pattern. The maximum UF rate in any programme did not exceed 1.5 times the average rate.

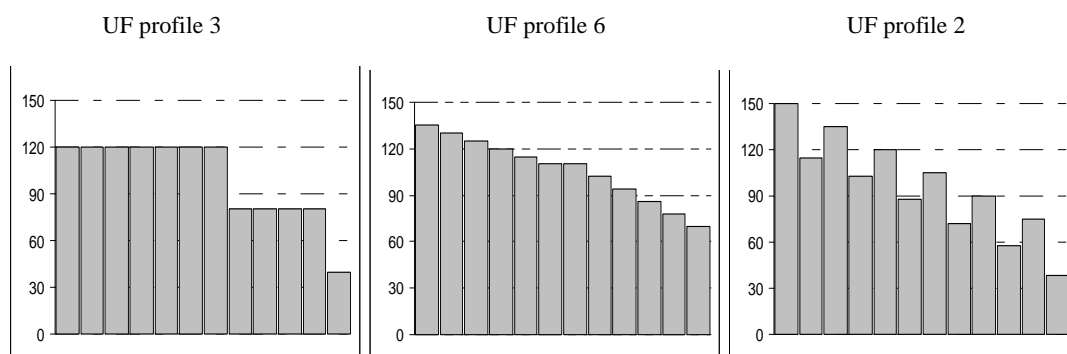


Figure 5.1: UF profiles

Dialysate Sodium Ramping

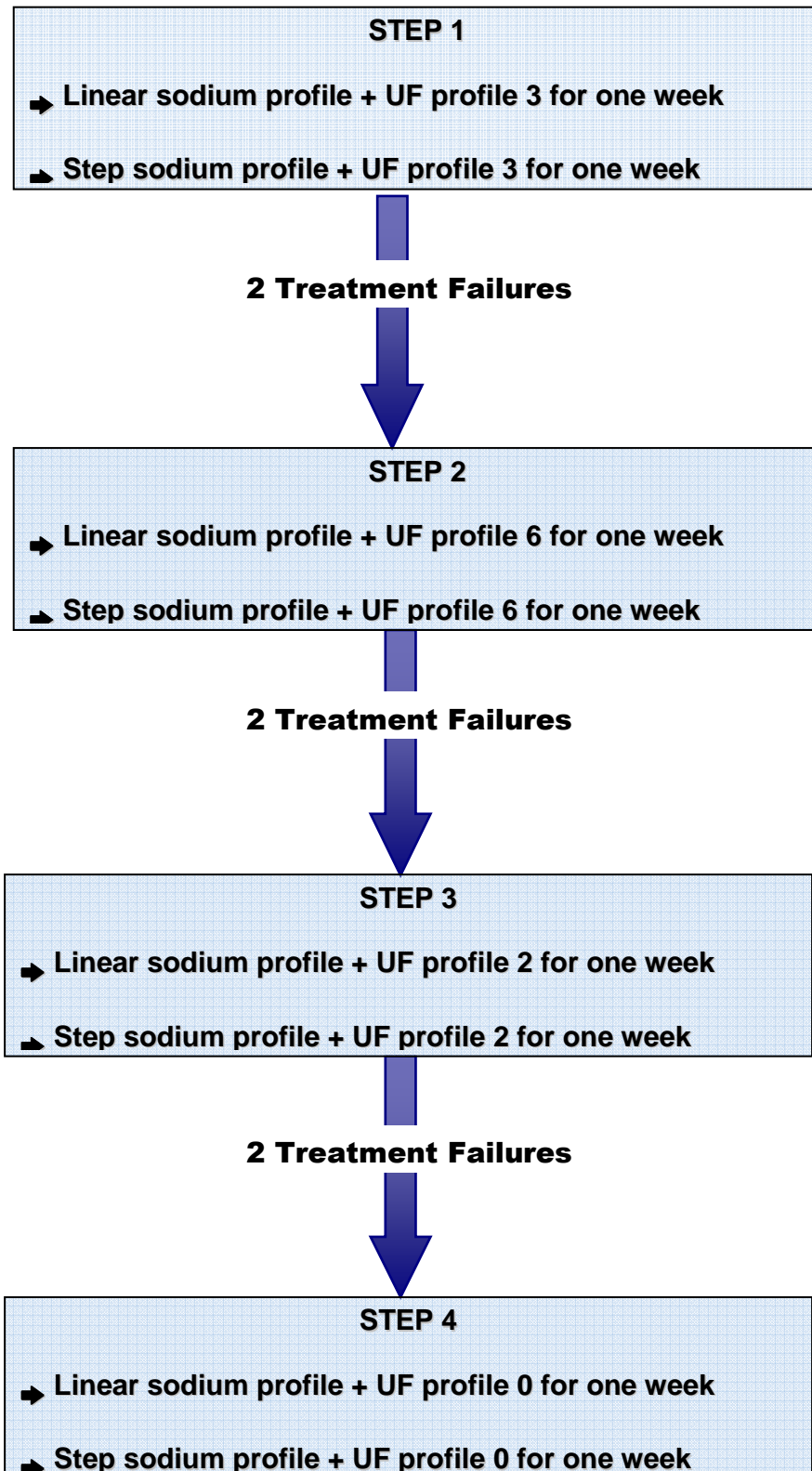
All standard treatments were prescribed a universal dialysate sodium gradient of 148mmol/l at the start of dialysis, ending with a concentration of 138mmol/l. During the linear sodium profile the dialysate sodium was decreased at a linear but constant rate to the final concentration. During the step profile the starting dialysate sodium was continued until the last 30 minutes of dialysis and then dropped in one step to the final concentration.

Study Protocol

A step wise approach to sodium and UF profiling was introduced for all the patients. Step 1: linear sodium profile + UF profile 3 for one week, followed by one week of step sodium profile + UF profile 3. The patient was then continued on the regimen with the least intradialytic symptoms, unless 2 treatment failures occurred, as defined below. In the event of two treatment failures the patient moved to Step 2, namely: linear sodium profile + UF profile 6 for one week, followed by one week of step sodium profile + UF profile 6. The patient again continued on the regimen with the least intradialytic symptoms, unless a further 2 treatment failures occurred. The patient then moved to

Step 3: linear sodium profile + UF profile 2 for one week, followed by one week of step sodium profile + UF profile 2. This was continued on the regimen with the least intradialytic symptoms, unless 2 treatment failures occurred. Finally Step 4: linear sodium profile + UF profile 0 (constant UF rate) for 1 week, followed by one week of step sodium profile + UF 0. This was continued on the regimen with the least intradialytic symptoms, unless 2 treatment failures occurred. At this point the patient exited from the study protocol.

Study Protocol



Treatment failure was defined as, i) premature discontinuation of the dialysis session, ii) intradialytic hypotension requiring a fluid bolus and iii) failure to achieve the dry weight only if the UF goal was less than or equal to 5% of the dry weight.

During each dialysis treatment the patient's heart rate, gross UF volume and BP was recorded hourly, at the time of an adverse event prior to any nursing intervention, and after recovering from it. A single BP reading was taken with an automated Dinamapp machine and a cuff adjusted for size. The first Task Force 5th percentile systolic blood pressure measurements, adjusted for age and sex⁸ were used to define intradialytic hypotension except in a single patient with co-existing panhypopituitarism in whom the cut-off systolic blood pressure was set at 75mmHg. In the event of a hypotensive episode UF was stopped and if the BP failed to recover after 15 minutes or the patient began to clinically deteriorate, a bolus of normal saline was administered.

In addition the following information was recorded during each treatment: i) description of intradialytic symptoms, ii) nature of any dialysis nurse intervention, iii) changes to the UF rate, and iv) administration of mannitol, blood products, or fluid boluses. At the end of the dialysis treatment the patient's weight and final UF volume was recorded. The dry weight was assessed monthly by a clinical assessment combined with a review of post-dialysis weights at which the patient displayed no symptoms indicative of under-hydration at the end of their treatment.

Outcome Measures

The outcome measures were categorized into 4 distinct groups:

OUTCOME 1 - occurrence of intradialytic symptoms and/or temporary suspension UF

OUTCOME 2 - administration of saline bolus and/or episode of hypotension

OUTCOME 3 - success in achieving the desired dry weight

OUTCOME 4 - UF volume expressed as a percentage of the dry weight calculated from the gross UF volume as the denominator

The primary endpoints were a comparison of sodium ramping and UF profiles 2,3 and 6 against the defined outcome measures and to determine the effects of intradialytic mannitol on these outcomes. The secondary endpoint was determining the volume of UF that was achievable by our standardized dialysis prescription. Polyuric patients were excluded from the analyses for OUTCOMES 3 and 4.

Statistical Analyses

All values of continuous variables were presented as mean \pm standard error or 95% confidence interval. A paired t test was used to determine whether there were significant differences between continuous variables at the 95th confidence interval. The incidence of observed events was expressed as a percentage, dividing the number of sessions during which an event occurred over the total number of sessions. For a more robust statistical comparison of the impact of the different treatments on outcome, a repeated measures Generalized Estimating Equations model was fitted to the data to account for the internal correlation structure of the data as a result of having repeated measures per subject. Treatment comparisons of linear versus step, 4 different sodium profiles, UF profile 0 versus 2, 3 and 6 and mannitol versus no mannitol were analysed and expressed as an odds ratio. A repeated measures ANOVA model was fitted to the percent dry weight data, our only continuous outcome. All statistical tests were two tailed with a p-value less than or equal to 0.05 taken to indicate significance.

5.3.2 Children prone to dialysis failure

Patients

During the previous study any child that had premature discontinuation of their dialysis treatment at minimum once weekly, on 3 separate occasions per treatment month, was selected. Of the 11 children, 6 were identified as being prone to severe intradialytic symptoms or hypotension and recruited for this study. The patient demographics are shown in Table 5.2. Ethics approval for this study was granted by the local research ethics board and informed consent was obtained from patients or their guardians.

Dialysis Prescriptions

All patients were dialysed against the standardised HD prescription for 3 hours 4 times/week or 4 hours 3 times/week using high flux membranes with dialysis flow rates between 200 to 650mls/min and blood flow rates adjusted to provide an estimated urea clearance of 4mls/kg/min. All patients were dialysed against 35mmol/l bicarbonate with a small quantity of acetate in the acidic component to stabilise the dialysate, 1.25mmol/l calcium solution and decreasing sodium profiles of 145-148mmol/l at the onset falling to 135-138mmol/l in a step-wise manner. The dialysate temperature was set at 37.5°C and treatments were programmed using a constant UF (UF profile 0).

All 6 patients underwent a trial of prophylactic mannitol and sequential dialysis.

Mannitol was given if the pre-dialysis plasma urea concentration was greater than 35mmol/l or if the patient experienced symptoms suggestive of dialysis dysequilibrium (severe headaches or altered levels of consciousness) on at least two separate occasions during previous dialysis treatments. For these patients 1g/kg mannitol was administered intravenously during the first hour of the first weekly dialysis session or 0.5g/kg during

two dialysis sessions per week. Mannitol was diluted in saline using 50mls of normal saline per 10g of mannitol. In children with repeated episodes of UF failure sequential dialysis was prescribed at the start or end, for 30 minutes during 3hr treatments or 60 minutes during 4hr treatments.

Table 5.2: Children prone to dialysis failure: patient demographics

Patient	Age	Primary Renal Disease	Co-morbidities	Urine Output (mls/kg/d)	Cardiac Echocardiogram [Antihypertensives]
1	11	Membranous glomerulonephritis	Developmental delay Syndromic Bone marrow suppression Panhypopituitarism	0	Normal [None]
2	16	ANCA positive glomerulonephritis	Absence seizures Poor adherence	0	Mild septal LVH [Amlodipine & Atenolol]
3	7	? Nephronophthisis	G6PD deficiency Hepatic fibrosis Subdural effusions with cerebroperitoneal shunt in-situ Intradialytic hypertension	2.9	Normal [Atenolol & Enalapril]
4	15	Hypo-complementemic glomerulonephritis	Biliary hypoplasia Failed liver transplant Splenomegaly & portal hypertension. Recurrent haematemesis secondary to oesophageal varices Pancytopenia Scurvy and malnourished	0.2	Mild concentric LVH [None]
5	14	Autosomal recessive polycystic kidney disease	Caroli's disease with hepatic fibrosis & retinal dystrophy Splenomegaly & portal hypertension Pancytopenia	0	Normal [None]
6	11	Solitary ectopic dysplastic kidney	Female hypospadias Poor adherence ASD, VSD Scoliosis	1.8	Small restrictive VSD. No LVH [None]

VSD: ventricular septal defect

ASD: atrioseptal defect

LVH: left ventricular hypertrophy

Study Protocol

During dialysis the patient's heart rate and BP was recorded hourly throughout treatment, at the time of symptoms and upon recovery. The first Task Force 5th percentile systolic BP measurements⁸ defined intradialytic hypotension except in Patient 1 whose cut-off systolic BP was set at 75mmHg. In the event of a hypotensive episode UF was stopped and if the BP failed to recover after 15 minutes or the patient began to clinically deteriorate, a bolus of normal saline was administered. At the end of the dialysis treatment the patient's weight and final gross UF volume was recorded. The dry weight was assessed monthly and qualified from a clinical assessment combined with a review of the post-dialysis weight and the onset of symptoms indicative of under-hydration following dialysis.

Outcome Measures

The outcome measures were categorized into 3 groups:

OUTCOME 1 - intradialytic symptoms (abdominal pain, cramps, headaches, loss of consciousness or change in behaviour)

OUTCOME 2 - hypotension or premature discontinuation of dialysis, due to persistence of hypotension/ symptoms in spite of a single fluid bolus

OUTCOME 3 - percentage dry weight removed (calculated as gross UF volume divided by the estimated dry weight).

Statistical Analyses

All values of continuous variables were presented as mean \pm standard error. A paired t test was used to determine whether there were significant differences between continuous variables at the 95th confidence interval. For a statistical comparison of the

impact of the different treatments on outcome, a repeated measures Generalized Estimating Equations model was fitted to the data to account for the internal correlation structure of the data as a result of having repeated measures per subject. A repeated measures ANOVA model was fitted to the percent dry weight data, our only continuous outcome. All statistical tests were two tailed with a p-value less than or equal to 0.05 taken to indicate significance.

5.4 Results

5.4.1 Prevalent chronic HD patients

A total of 506 dialysis treatments were reviewed with 162/506 (32%) from polyuric patients. A linear sodium profile of 148mmol/l to 138mmol/l was used in 219/506 (43%) treatments and a step profile in 287/506 (57%). UF profile 2 was used in 103/506 (20%) treatments, UF profile 3 in 137/506 (27%) treatments, UF profile 6 in 19/506 (4%) treatments and no UF profile in 287/506 (57%) treatments. Mannitol was prescribed in 48/502 (9%) treatments.

The prevalence of intradialytic symptoms (OUTCOME 1) was 26%. Intradialytic hypotension or administration of a fluid bolus (OUTCOME 2) occurred in 19%. The desired dry weight was achieved in 124/344 (36%) treatments from non-polyuric patients. Using our standardized dialysis prescription combining sodium and UF profiling and intra-dialytic mannitol we achieved UF goals ranging from 3.2% to 9.7% of the dry weight (OUTCOME 4). Analysed individually the mean UF volume for all the interventions were greater than the current recommendations of 5% from the

European Haemodialysis Guidelines¹⁵² with mannitol achieving the highest mean UF volume (see Table 5.3).

The overall treatment failure rate was 33% (167/506 treatments). Treatment failure due to premature discontinuation of the dialysis session occurred in 20/506 treatments and of these 5 were due to hypotension episodes and 15 due to intradialytic symptoms. Failure due to the development of intradialytic hypotension requiring a saline bolus occurred in 37/506 treatments. Finally 115/506 treatments failed to achieve the desired dry weight, despite a target UF goal less than 5%. The treatment protocol resulted in significant morbidity in one patient who had a history of panhypopituitarism, bone marrow failure and was prone to hypotensive episodes. He became unconscious during 4 dialysis treatments. This was associated with marked hypotension and bradycardia and was thought to be secondary to a Bezold-Jarisch reflex. Owing to the severity of his symptoms he was excluded from the protocol prematurely but his data was included and analysed up to and including the 4th episode. One patient developed intradialytic symptoms and interdialytic fatigue with UF profile 6 on two consecutive dialysis sessions and refused further treatments with UF profile 6.

Linear Versus Step Sodium Ramping

There was no significant difference between linear and step sodium ramping and the onset of intradialytic symptoms. Compared with the step profile the linear profile increased the odds of hypotensive episodes or premature discontinuation of treatment by 27% (see Table 5.4). The likelihood of achieving the dry weight was no different between the step and linear sodium profiles and the mean UF volume for both was virtually identical at 5.4% of estimated dry weight (see Table 5.3).

UF Profiles

The UF profiles were no better than a constant UF rate (UF profile 0) in preventing intradialytic symptoms, hypotensive episodes or premature discontinuation of dialysis (see Table 5.4). UF profile 2 was the least effective in achieving the desired dry weight, reducing the odds by 40% when compared to a constant UF rate, reducing the odds by 60% compared with profile 3 and reducing the odds by 36% when compared against UF profile 6. The latter was not statistically different and neither were the remaining UF profile comparisons. Profile 3 increased the odds of achieving the dry weight by 50% compared with a constant rate and UF profile 6 was virtually identical to a constant UF rate (see Table 5.4). The mean UF was however higher with all 3 profiles compared to UF profile 0, but only the difference between profile 2 and 0 were statistically significant (Table 5.3). Therefore all 3 UF profiles had mean UF volumes greater than 5% of the dry weight but none of them significantly increased the odds of achieving the dry weight.

Mannitol

Compared to dialysis treatments without mannitol, the administration of mannitol reduced the odds of intradialytic symptoms by 64% ($p < 0.05$) but did not improve the odds of preventing intradialytic hypotension or achievement of the desired dry weight (see Table 5.4). The mean UF volume was statistically greater with mannitol compared to those without, with a mean of 6.2% of the dry weight (see Table 5.3).

Table 5.3: Comparison of the Percentage Dry Weight Removed

	All patients excluding those with polyuria Mean [95% CI]
Linear sodium	5.41 [4.97 – 5.86]
Step sodium	5.37 [4.96 – 5.78]
UF profile 0	5.03 [4.68 - 5.38] ^A
UF profile 2	5.99 [5.49 – 6.49]
UF profile 3	5.61 [4.98 – 6.25]
UF profile 6	6.11 [5.26 – 6.96]
Mannitol	6.18 [5.39 – 6.9] *
OVERALL	5.39 [5.07 – 5.71]

A : the difference between UF profile 0 and profile 2 was significant (p<0.05)

* : the difference between mannitol versus no mannitol was significant (p<0.05)

[For the remainder the differences were not statistically significant]

Table 5.4: Odds ratios of defined outcomes against each dialytic intervention

	OUTCOME 1	OUTCOME 2	OUTCOME 3
Linear v Step sodium	1.61 (p=0.10)	1.27 (p=0.05)	1.25 (p=0.54)
UF profile 2 v 0	1.58 (p=0.16)	0.77 (p=0.28)	0.60 (p<0.05)
UF profile 3 v 0	1.66 (p=0.28)	0.91 (p=0.81)	1.46 (p=0.24)
UF profile 6 v 0	1.47 (p=0.6)	1.50 (p=0.21)	0.95 (p=0.82)
UF profile 2 v 3	0.95 (p=0.87)	0.85 (p=0.78)	0.41 (p<0.05)
UF profile 2 v 6	1.08 (p=0.9)	0.51 (p=0.23)	0.64 (p=0.07)
UF profile 3 v 6	1.13 (p=0.74)	0.61 (p=0.11)	1.54 (p=0.14)
Mannitol v no mannitol	0.36 (p<0.05)	1.06 (p=0.89)	1.15 (p=0.82)

Outcome 1: Odds of intradialytic symptoms

Outcome 2: Odds of hypotensive episode and /or administration of saline bolus

Outcome 3: Odds of successfully achieving the desired dry weight

5.4.2 Children prone to dialysis failure

Of 399 dialysis treatments intradialytic mannitol was given in 57 (17%) and sequential dialysis in 44 (11%). Intradialytic mannitol significantly increased mean treatment UF volume (see Table 5.5), 86% of the treatments achieved UF volumes greater than average for that individual patient and one third achieved their dry weight. Mannitol halved the odds of intradialytic symptoms and hypotension/premature discontinuation of dialysis (see Table 5.6). Sequential dialysis also halved the odds of intradialytic symptoms (see Table 5.6). Intradialytic hypotension developed in 50% of the treatments but dialysis was only prematurely discontinued in 2% of treatments and 2 out of 3 treatments achieved UF volumes greater than the average for an individual patient (see Table 5.5).

Table 5.5: Prevalence rates of intradialytic morbidity and achieving the desired UF goal with intradialytic mannitol and sequential dialysis

Intervention	Symptoms	Hypotension	Premature discontinuation of treatment	Dry Weight Achieved	UF as Percentage Dry Weight Mean [95% CI]
Mannitol	6/57(11%)	3/57 (5%)	3/57 (5%)	* 9/29(31%)	5.55 [5.04 – 6.06]
Sequential	1/44 (2%)	23/44 (53%)	1/44 (2%)	18/44 (41%) 10/21(48%)	4.23 [3.66 – 4.80]

† Average UF volume for each patient was calculated from the total number of dialysis session over a 6 month period.

* excluding polyuric patients

Table 5.6: Impact of mannitol and sequential dialysis on intradialytic symptoms and hypotension

	OUTCOME 1	OUTCOME 2
Mannitol v no mannitol	0.44 (p<0.05)	0.56 (p<0.05)
Sequential v no sequential	0.47 (p<0.05)	2.45 (p<0.05)

Outcome 1: Odds of intradialytic symptoms

Outcome 2: Odds of premature dialysis discontinuation and/or administration of saline bolus and/or episode of hypotension

Table 5.7: Chi-squared analysis of interventions mannitol and sequential dialysis and outcomes

	OUTCOME 1	OUTCOME 2
Mannitol	2.64 (p=0.10)	0.35 (p=0.18)
Sequential	1.16 (p=0.20)	1.61 (p=0.28)

Degrees of freedom: 1

p value is the probability of the null hypothesis being true

Outcome 1: Odds of intradialytic symptoms

Outcome 2: Odds of premature dialysis discontinuation and/or administration of saline bolus and/or episode of hypotension

In patient 1 the odds of intradialytic hypotension was 23 times greater than the group risk. His pre-dialysis systolic BP ranged between 85-105mmHg and his interdialytic weight gain frequently exceeded 5% his dry weight. The patient's predisposition for hypotension was often during the second hour of dialysis and was often associated with bradycardia. Sequential dialysis reduced intradialytic symptoms but not hypotension. Twice weekly mannitol reduced the odds of symptoms and hypotensive episodes but the

UF potential was unchanged. As an isolated case I then elected to trial intradialytic midodrine. In the event of a declining BP 2.5mg of oral midodrine was given. If the BP failed to improve within 30 minutes or fell below 75mmHg a further 2.5mg dose was given. A cut-off of 7.5mg total dose was applied per 3 hour treatment and no midodrine was given in the final 30 minutes irrespective of BP. On using intradialytic midodrine no intradialytic symptoms were observed and the mean treatment UF volume increased from 3.74% to 3.96%, achieving higher than average UF volumes in 95% of the treatments and the desired dry weight in one third of the treatments (see Table 5.6). During 18 of 20 observed dialysis sessions a 2.5mg oral dose of midodrine produced a 10-15mmHg increase in the systolic BP within 30 minutes of administration and no adverse effects were reported in the intradialytic or interdialytic period.

5.5 Discussion

The uraemic milieu impairs compensatory responses to haemodynamic stress with ineffective venoconstriction, inadequate cardiac refilling, reduced plasma refilling and activation of the sympathoinhibitory Bezold–Jarisch reflex leading to sudden hypotension¹⁵³. In paediatrics more often than not we are faced with the additional challenge of large UF goals. During standard 4 hour HD sessions this combination can result in decompensation and morbidity. I have shown both in prevalent dialysis patients and in high risk children that are prone to hypotension that manipulation of conventional HD prescriptions can improve the dialysis experience.

Children may not understand or appreciate the long-term implications of chronic hypervolaemia and are often non-adherent to their fluid restrictions. The excess fluid

accumulates both in the intravascular and extravascular compartments, but only the former is amenable to UF during dialysis. During their treatments they often do not voice the onset of symptoms until they are severe or associated with hypotension. Children have compliant high capacitance vessels and hypovolaemia may occur suddenly with little warning. This reduces the opportunity to change the UF rates before the intravascular volume becomes compromised. As a result, cautious UF goals of 5% of the dry weight have been recommended¹⁵². In paediatrics, Jain et al were the first to challenge this recommendation by introducing the concept of adjusting UF rates according to changes in RBV⁴³. They reported reduced dialysis associated morbidity providing the UF volumes did not result in a blood volume change greater than 8% in the first hour and 12% over the dialysis session. In comparison I have demonstrated that through the use of dialysis regimens combining sodium ramping, UF profiles and intravenous mannitol, UF volumes of up to 9% of the dry weight can be achieved.

The intravascular compartment is continuously changing during dialysis as fluid is removed by UF but refilled from the interstitial compartment. The total circulating blood volume during a dialysis treatment is therefore greater than that of a normovolaemic individual with a significant inter-patient and intra-patient variation in the pattern of RBV change¹⁵¹. Therefore any dialytic measure that promotes vascular refilling or improve cardiovascular stability should in theory help to restore normovolaemia and increase the UF potential in dialysis patients. Sodium profiling provides a diffusive sodium influx at the start of dialysis to counterbalance the rapid decline in plasma osmolarity from clearance of uraemic solutes, ending with a low dialysate sodium concentration to encourage diffusive clearance of the sodium load. Compared with a constant dialysate sodium concentration, ramps have been associated with increased stability of the intradialytic blood volume and reduced intradialytic

cramps and interdialytic fatigue in adults^{78, 127} and in older children⁷⁸. This is in keeping with the findings of this study, whereby the odds of intradialytic hypotension were reduced with a step ramp compared to a linear ramp. This is most likely due to a longer period of increased plasma osmolarity that promoted vascular refilling. There is in theory a price to be paid with a potential of chronic sodium loading driving thirst, chronic water expansion and increasing interdialytic weight gain. In this study no long term data pertaining to interdialytic symptoms or weight gain was measured.

The RBV at the point of decompensation shows large intra-patient and inter-patient variability but the vascular refilling capacity is always proportionately higher when the interstitial volume is expanded. This provides the rationale for UF profiles. Donauer et al reported a reduction in symptomatic hypotension episodes on profiles with decreasing UF rates with time on HD⁸¹. The outcomes of this study have been less favourable, I found no difference between profiling and a constant UF rate in preventing intradialytic symptoms or hypotension and in fact found that UF profile 2 reduced the odds of achieving the desired dry weight. The mean UF volumes were greater in the UF profile groups compared with treatments applying constant UF rates, but the gain was insufficient to increase the ability to achieve the desired dry weight. These contradictory results may be a reflection of the small sample size that was under-powered to reveal small differences. Alternatively the results are valid and are indicative of the problem of high UF rates that are characteristic to UF profiles. These periods of higher than average UF rates, or variable duration may exceed the body's capacity to compensate, offering very limited reserve for variations in refilling capacity and thus at best only achieve minor gains in dialysis quality. In truth attempting to address the issue of large UF goals with techniques focusing on UF rates alone without consideration to refilling rates are in

reality destined to fail. In comparison automated RBV biofeedback techniques or more simply, RBV driven algorithms⁸⁹ that adjust UF rates according to RBV changes are successful in achieving equivalent or higher UF volumes with reduced cardiovascular instability.

Mannitol is a drug traditionally used in the management of dialysis disequilibrium as it can artificially increase plasma osmolarity. In prevalent dialysis patients, treatments prescribed mannitol achieved the highest mean UF volumes coupled with a significant reduction in the odds of symptoms, hypotensive episodes and the premature discontinuation of dialysis. Such positive outcomes were mirrored in the patients prone to hypotension. Mannitol requires dilution in saline prior to administration. Every 10g of mannitol is diluted in 100mls of normal saline and thus concurrently delivers 15mmol of sodium to the intravascular compartment during the infusion. Therefore one could simply attribute its benefits to the fluid bolus that is inadvertently given and the increased gross UF volumes could be the result of filtering this fluid load. The counter-argument to this is that the benefits of mannitol exceed that of a saline bolus. Mannitol also differs in the fact that it is an osmotically active solute that unlike sodium does not leak into the interstitium and thus provides a more sustained oncotic effect. On a note of caution this osmotic effect could theoretically be counter-productive as it runs a risk of inducing thirst in the interdialytic period with resultant escalating hypervolaemia. An alternative explanation to mannitol's success is that it successfully treated milder degrees of disequilibrium, thus allowing treatments to proceed to completion. The true incidence of dysequilibrium is unknown but children, by virtue of their age, are deemed high risk. One patient also had an additional risk from co-existing neurological disease. It is also conceivable that within this context, the benefits of mannitol may have been

more pronounced as children are less likely to communicate symptoms until they are severe.

Abnormal baroreflex sensitivity, altered vascular physiology, reduced coronary flow reserve are integral to cardiovascular decompensation during dialysis^{150, 154}. The resultant effect is failure to preserve the central blood volume and myocardial dysfunction secondary to a reduction in global and regional myocardial blood flow⁶⁵. During HD, UF activates sympathetic vasoconstriction, reducing skin blood flow and therefore heat exchange, with a direct correlation between UF volume and the amount of heat gained⁹⁷. During isolated filtration there is significant cooling over the extracorporeal circuit and this attenuates the increase in core temperature^{98, 155}. In patients prone to hypotension short-periods of sequential dialysis reduced intradialytic symptoms and half of the patients achieved their dry weight by the end of dialysis, but the risk of hypotension was unchanged. If we are to believe that the benefits of sequential dialysis are related to cooling then one can understand how short bursts of isolated UF have limited gain as the remainder of the dialysis time is spent at dialysate temperatures of 37.5°C. This would negate any changes in core temperature that may have been achieved during sequential dialysis. Furthermore it is probable that with longer periods of sequential dialysis or by reducing the dialysate temperatures during the remainder of the treatment outcomes may have improved further.

Midodrine was not part of the study protocol but was used as rescue therapy in one of the patients and hence deserves to be part of this discussion. Midodrine is a prodrug of desglymidodrine, a specific α -1 adrenergic agonist that increases intradialytic BP by mediating constriction of both arterial and venous capacitance vessels, thus preventing

venous pooling while supporting central BP. Oral administration in our patient achieved peak levels within 1hr and I saw no evidence of prolonged hypertension beyond the period of dialysis in spite of pharmacokinetic data indicating a half-life of 3hrs. Minor adverse reactions such as scalp paraesthesia, heartburn, flushing, headache, weakness and neck soreness have been described¹⁵⁶ but no such adverse effects were witnessed. Adult nephrologists have the greatest experience with midodrine and report variable success but our results mirror those of Blowey et al reporting a benefit in an 18 year old¹⁵⁷. This single experience in a very difficult patient was very encouraging and certainly places midodrine in a position of priority for future research.

5.6 Study Limitations

The patient cohort was a small, heterogeneous group. In addition by virtue of the study protocol the exposure to the different interventions also varied between patients reducing intervention specific numbers further. Therefore my findings may be a reflection of the fact that the study was underpowered for small differences between the interventions and the results may have been different in a larger cohort. In a bid not to restrict numbers further all prevalent dialysis patients were recruited, including those with congenital heart defects. We know that the structural and physiological properties of the cardiovascular system are susceptible to change with disease. All of the cardiac patients were found to be susceptible to intradialytic symptoms and hypotension and hence they may have introduced a bias in the study of prevalent dialysis patients. Their inclusion within the second study with other high risk patients was probably more appropriate and encouragingly the results were no different. In paediatric HD, the prevalent dialysis patients tend to be children unsuitable for peritoneal dialysis, with

several co-morbidities, therefore even from the very onset of this study a selection bias was introduced. This also raises an important question on whether the baseline risk for cardiovascular compromise in prevalent HD patients differs from stable uncomplicated uraemic children.

Within the study protocol it was impossible to control the UF prescription per dialysis treatment as this would have compromised patient well being. However there is a clear relationship between UF volumes and the risk of intradialytic morbidity. The problem is confounded further by the fact that tolerance to UF varies between patients and between treatments as illustrated in Chapter 3. Therefore even if statistical adjustments of the analyses for UF volumes were attempted this bias could not have been eliminated in this study.

This is a preliminary study and being conscious of time and the relatively quick turnover of patients within paediatric dialysis units I did not elect to introduce interventions separately. For example sodium ramping was part of the standard prescription in the study of patients prone to hypotension and was used in combination with the UF profiles in the prevalent dialysis patients study. As a consequence it is hard to know whether the results achieved were exclusively attributable to the intervention in question or due to the synergistic effect of all the interventions that were present per dialysis treatment.

Finally on a number of occasions in the discussion I have raised concerns of the long term effects of some of these interventions such as sodium profiling and intradialytic mannitol and the theoretical risk of chronic volume expansion. Follow up within this

study was short and data primarily concentrated on the intradialytic period and not the interdialytic period. In the battle against UF failure, preventative measures that limit salt and water intake are equally important, if not more important than intradialytic strategies aimed at treating salt and water excess. The lack of data on the long-term consequences of these interventions is a shortcoming of this study and is certainly an area thus needs to be explored in future studies.

5.7 Conclusion

During standard 4 hour HD regimens the evidence for the cardiovascular burden of HD is growing stronger and with it the urgency for change in the way we dialyse our patients. Improving dialysis failure is essential for patient well-being and will only be achieved following a better understanding of the underlying mechanism. Through a multidirectional approach, utilising strategies that improved plasma refilling and supported the central blood volume I have demonstrated an attenuated risk of intradialytic morbidity in both prevalent dialysis patients and children that are prone to hypotension. In our most resistant case oral midodrine was the only viable rescue option, nonetheless experience with midodrine in paediatrics is still very limited and its efficacy needs to be validated in larger, randomised trials prior to recommending it for general use.

Chapter Six

Thesis Summation

Paediatric HD patients are typically children that are unsuitable for home peritoneal dialysis, the default mode of dialysis, owing to social and/or medical co-morbidities. Whether this translates to a higher baseline risk of cardiovascular disease is unknown but what has become apparent from this research are the similarities in adverse outcomes related to in-centre, conventional HD sessions between children and adult HD patients.

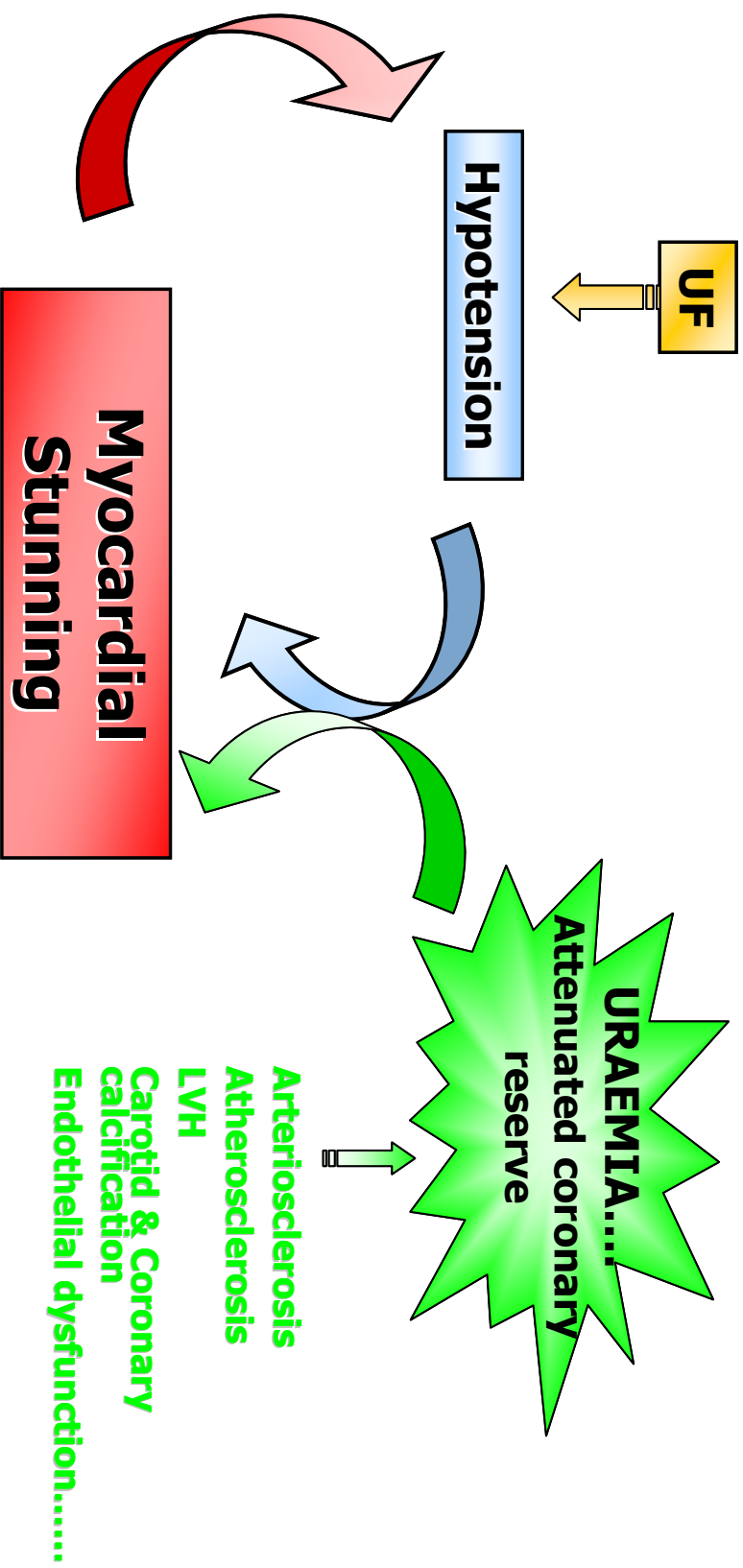
During conventional 4 hour paediatric HD treatments the prevalence of intradialytic hypotension ranged between 20-30%, a rate that is comparable to adult HD patients. In an attempt to restore euvolaemia at the end of each of their dialysis treatments UF goals as high as 9% of the dry weight were successfully attempted in the children but this was associated with a RBV reduction of 30%. More commonly UF goals of up to 6% of the dry weight were prescribed and this resulted in a marked inter- and intra-patient variability of RBV change that was not predictive of the onset of adverse intradialytic events. This supports the concept that decompensation during HD is not just related to changes in intravascular blood volume but other factors are also important. Tachycardia, a signal for the onset of compensatory mechanisms, and the severity of RBV change during the first hour of dialysis were significantly predictive of impending intradialytic symptoms or hypotension.

It is clear from this data that conventional HD places a significant haemodynamic stress on the child and one that triggers compensatory cardiovascular mechanisms aimed at maintaining circulation adequacy. However the nature of these responses varied between the patients studied. Nonetheless a pattern emerged. The cardiac output was more dependent on a chronotropic response than ionotropic response while the

intradialytic BP mirrored changes in peripheral vascular resistance. This also raised a suspicion that uraemic children have an attenuated ability to increase myocardial contractility during the course of HD.

In children aged between 1 and 17 years there is functional and biochemical evidence of cardiac injury during conventional 4hour HD manifesting as transient, regional LV myocardial dysfunction in association with an elevation of plasma cardiac enzymes in one quarter of patients. The degree of dysfunction was related to the UF volume and intradialytic blood BP. In addition the percentage decline in LV function in the longitudinal axis was predictive of changes in systolic BP during dialysis. I postulate that the characteristic cardiovascular phenotype in HD patients predisposes to significant demand ischemia as illustrated in Figure 6.1. Conventional 4 hours HD is associated with increasing tachycardia and hypotension with a potential to cause an acute fall in coronary blood flow. Ordinarily this physiological stress is met and overcome by a complex network of autoregulatory mechanisms within the coronary circulation that supports and maintains an appropriate blood supply to the heart. However owing to the underlying constellation of cardiovascular disease that is typically found in uraemic children, the coronary reserve flow is impaired. Thus in the presence of an increased metabolic demand, such as dialysis, the limited ability to increase the oxygen supply to the heart results in a demand supply mismatch. Ischaemia prevails and this manifests as regional myocardial dysfunction. Owing to the design of the study it is impossible to decipher what factor takes the leads, the hypotension or the myocardial dysfunction. Regardless of the initiator, it is highly probable that the two are self-perpetuating.

Figure 6.1: Postulated mechanisms behind the evolution of myocardial stunning and the relationship with intradialytic blood pressure



The technique of speckle tracking 2D strain was superior to assessments of regional wall motion activity in detecting acute abnormalities in regional myocardial function. 2D speckle tracking was both angle and translation independent and was therefore less influenced by intra-observer variability between images, improving its accuracy. It also provided two parameters of assessments, the peak strain and inter-segmental synchronicity index. The latter is particularly sensitive in detecting ischemic cardiac injury and therefore in this setting has the potential for becoming a screening tool, looking for early evidence of dialysis induced cardiac injury and with it a window of opportunity to intervene before the myocardial injury becomes severe.

The evidence for the cardiovascular burden of HD is growing stronger and with it the urgency for change in the way we dialyse our patients. Armed with greater details of the altered physiological responses during dialysis, a more directed approach to managing intradialytic morbidity is conceivable. During paediatric HD, patients are largely able to mount a tachycardic response but support is required to increase peripheral vascular resistance, expand the central blood volume and augment myocardial contractility. Sodium profiles and intradialytic mannitol encourage plasma refilling, sequential dialysis prevents blood from being diverted away from the central blood volume and midodrine increases vascular resistance. All four interventions were shown to be effective in moderating intradialytic symptoms and hypotension, midodrine and sequential dialysis exclusively in high risk, hypotension prone patients.

Chapter Seven

Future Work

All the research that has been reported in this thesis is based on studies of a small cohort of HD patients from a single centre. First and foremost the results require validation from larger scale, long-term studies. The haemodynamic study (Chapter 3) would benefit from a larger population base as this will allow the patients to be divided into relevant groups based on urine output, underlying renal disease and baseline risk of decompensation. These are factors that are likely to influence the compensatory response during dialysis and any information gained will provide additional insight into any variations that exist and help direct focused strategies to improve HD related morbidity.

The study examining the myocardial effects of dialysis (Chapter 4) was limited to the acute effects on the heart from single dialysis sessions. However both adult dialysis data and the model of coronary artery disease allude to the progressive nature of myocardial stunning. This strengthens the case for gaining long-term follow up data in children. In addition data following them longitudinally once they change renal replacement therapy, such as transplantation will provide invaluable information on the degree of reversibility of dialysis induced myocardial injury and the risk of myocardial injury between the different forms of renal replacement therapies.

The dialysis intervention study (chapter 5) measured the efficacy of various dialysis interventions in modifying intradialytic symptoms and prevalence of hypotension. One battle that is in the forefront of all nephrologists is that of salt and water balance. However in order to win, strategies have to be directed towards the interdialytic period as well as the intradialytic period that was exclusively examined

here. Interventions such as sodium profiles and intradialytic mannitol increase the osmotic load during dialysis and this may have a knock on effect on chronic fluid and BP management. Long-term follow up is required to ascertain the impact of these dialysis interventions on the immediate and late interdialytic period both in terms of patient symptoms and volume status. Furthermore this work could also be extended laterally by examining differences in RBV and dialysis induced myocardial dysfunction between the different interventions. Finally following on from the example set here and the success of midodrine in treating a very resistant case of intradialytic hypotension, its role in paediatric HD needs to be explored further. I would propose a randomised, cross-over trial of children prone to hypotension, supported by finometer, RBV change and regional myocardial function data.

This thesis has introduced the concept of myocardial stunning in uraemic children and now additional work is necessary to understand the extent of the problem within the paediatric nephrology population base. The non-invasive technique of 2D speckle tracking lends itself well to these investigations.

- I would like to start by investigating whether the chronicity of renal failure is important in medicating myocardial dysfunction. I plan to examine this by studying patients with acute renal failure on continuous renal replacement therapy.
- At present it is difficult to know whether 'uraemia' or the haemodynamic stress related to dialysis is the dominant factor in dialysis induced myocardial dysfunction. Peritoneal dialysis (PD) is a gentler form of dialysis that is generally not associated with a large haemodynamic burden. An investigation of

children on PD would provide further insight on the relationship between uraemia and myocardial stunning.

- At Great Ormond Street Hospital for Children, we have initiated plans to develop a paediatric home HD programme. Frequent HD has been shown to be superior to conventional HD both in fluid management, BP control, intradialytic haemodynamic stability and dialysis quality, but the mechanisms remain elusive. I would like to use this opportunity to explore the potential role of myocardial stunning in the reported cardiovascular advantages linked to this patient cohort.
- Sequential dialysis utilizes the principle of cooling to improve cardiovascular stability during paediatric HD but is adversely associated with sodium loading. Applied independently within conventional HD prescriptions, cooling of the dialysate has cardiovascular benefits but the duration and intensity of cooling is limited by the onset of symptoms related to feeling cold. I propose a randomised, cross-over study to determine the optimal paediatric dialysate temperature for abrogation of intradialytic morbidity without inducing adverse symptoms. This study could potentially provide a widely applicable and cost-effective intervention for reducing the cardiovascular burden that children carry into adulthood.

List of Abbreviations

2D	two-dimensional
AHA	The American Heart Association
ANCA	anti-neutrophil cytoplasmic antibodies
ANOVA	one-way analysis of variance
ARPKD	autosomal recessive polycystic kidney disease
BNP	brain natriuretic peptide
BP	blood pressure
CRP	C-reactive protein
cTnI	cardiac troponin-I
cTnT	cardiac troponin-T
CO	cardiac output
CAD	coronary artery disease
CKD	chronic kidney disease
CI	confidence interval
EF	ejection fraction
ESRD	end stage renal disease
FSGS	focal segmental glomerulosclerosis
hsCRP	high sensitivity C-reactive protein
HD	haemodialysis
HR	heart rate
IL-6	interleukin 6
LV	left ventricle
LVH	left ventricular hypertrophy

MBF	myocardial blood flow
NIVM	non-invasive blood volume monitors
PD	peritoneal dialysis
PET	photon emission computed tomography
ROC	receiver operating characteristics curve
RBC	red blood cell
RBV	relative blood volume
RWMA	regional wall motion abnormalities
SV	stroke volume
TPR	total peripheral resistance
UF	ultrafiltration

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